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ACTA PÆDIATRICA

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Acta Pædiatrica **44**: 507—512. Nov. 1955

From the Children's Hospital, University of Oslo, Norway
(Head: Professor LEIF SALOMONSEN)

Humoral Factors in Regulation of Reticulocyte Level and Erythropoiesis in Man

by MARTIN SEIP

The relationship between oxygen content in the inspired air and rate of erythrocyte formation has been realized since the studies of BERT (1882) and VIAULT (1890). MIESCHER (1893) postulated that the oxygen tension *in the bone marrow* directly regulates at least in part the production of red cells. However, intensive studies have failed to confirm this concept (HEILMEYER, GRANT & ROOT, MAGNUSSEN).

CARNOT & DEFLANDRE in 1906 were the first to postulate a humoral regulating mechanism. According to this theory reduced oxygen content of the blood produces an increased formation of erythropoiesis-stimulating substances in the body ("erythropoietines"). For a long time this theory was widely disputed, but a number of experiments now seem to have proven its validity, at least in certain animal species. The literature on this subject was reviewed in 1953 (SEIP). More recently, ERSLEV and coworkers and HODGSON & TOHA in well-controlled animal experiments have demonstrated the presence of erythropoietines in "anemic" plasma.

So far these humoral factors had only been demonstrated in animal experiments. The present report concerns the extension of observations on the humoral regulation of red cell formation to humans.

Material and Methods

The subjects in all cases were infants since limited amounts of suitable donor plasma were available and hence proportionately larger amounts could be given. Eleven studies were carried out on seven infants, having no blood disorders and normal reticulocyte levels for age. Plasma injected intravenously in amounts of 9–20 cc (2.6–6.7 cc/kg) was obtained from three sources: (a) normal adults showing normal levels of reticulocytes, (b) cord blood of normal newborn infants, (c) erythroblastotic infants during the first stages of a replacement transfusion. In some studies, fresh plasma was used, in others fresh frozen plasma kept a few days to weeks at -20°C. The blood was heparinized and typed, and Witebsky neutralizing substances were added if necessary. Plasma from infants with erythroblastosis was only given to Rh-negative babies.

The method for staining and counting reticulocytes has been described in detail elsewhere (1953). A slightly modified staining fluid consisting of brilliant cresyl blue 1 % and sodium citrate 0.4 % in normal saline was used. Capillary blood from the infants' heel was used for all counts. They were performed by the same observer (M. S.), counting 5,000 red cells per preparation. By this method, the blood of normal adults was found to contain 1–2.5 % reticulocytes with a standard deviation of 0.107 % when examinations were performed on the same day, and 0.152 % when they were performed over several days. From two to four pre-injection counts were performed. Because of the accuracy of this technique, relatively small changes in the reticulocyte content of the blood can be detected. Post-injection counts were done after 30 minutes, and, in most cases, after approximately 4, 24, and 48 hours.

Results and Discussion

The results of the eleven studies are shown in Table 1 and Figure 1. It can be seen that there was no significant effect on the reticulocyte count resulting from the injection of normal adult plasma into three different infants (Cases 1, 2, 3).

However, cord plasma from normal newborns, all of whom have a markedly increased erythropoiesis and high reticulocyte counts (about 5 %) at birth, produced a significant reticulocytosis four times in these same three infants.

A similar significant rise followed injection of plasma from infants with erythroblastosis in four additional infants (Cases 4, 5, 6, 7).

The increase in reticulocyte levels produced in the present studies was of short duration with a maximum increase between 30 minutes and 5 hours after injection and a return to pre-injection levels in 24 to 48 hours. Presumably, if the data from animal experiments are applicable to humans, repeated injections would have produced a more marked and more sustained reticulocytosis.

In previous studies (1953) plasma from patients with high reticulocyte levels was injected into normal adults. Relatively small amounts of plasma were given, 20–30 cc per injection. Plasma obtained from infants with erythroblastosis produced a mild, though statistically significant increase in the reticulocyte content of the blood, amounting to about 20 % of the pre-injection level per 20 cc of plasma injected. Plasma from patients with congenital spherocytosis or pernicious anemia under reticulocyte crisis had no evident effect, probably because of the lower concentration of the humoral factors in these cases. Injections of normal adult plasma had no effect on the reticulocyte level.

A direct relationship was found both in the observations in adults and in the present series between the original reticulocyte count of the recipient and the increase caused by the plasma infusion, as shown in the Table.

TABLE 1

Effect on the reticulocyte level of injections of different kinds of plasma into small infants without blood disorders.

Inf. No.	Age	Weight in kg	Clinical diagnosis	Dose injected		Pre-injection retic. level per mille	Maximum rise per mille	Rise per 20 cc of plasma in per cent of pre-injection level
				cc	cc/kg			
			Normal adult plasma					
1	3 wks.	3.5	Mongolism	18	5.1	6.4	0	0
2	10 d.	3.5	Mongolism	18	5.1	3.6	0	0
3	10 mo.	6	Cerebral defect	20	3.3	13.0	1.0	(8 %)
			Cord plasma from normal newborns					
1	2 wks.	3.5	Mongolism	9	2.6	4.6	4.4	(213 %)
1	4 wks.	3.5	Mongolism	15	4.3	5.6	4.0	95 %
2	2 wks.	3.5	Mongoljsm	15	4.3	2.4	1.4	77 %
3	10 mo.	6	Cerebral defect	16	2.7	12.6	3.6	36 %
			"Erythroblastotic plasma"					
4	18 d.	3	Multiple defects	20	6.7	11.8	6.6	56 %
5	2 wks.	3.5	Hydrocephaly	20	5.7	4.4	5.0	114 %
6	7 mo.	5	Mucoviscidosis	20	4.0	12.2	6.0	49 %
7	10 wks.	4	Hydroceph. following meningitis	15	3.8	24.2	10.0	55 %

This is presumably because the reticulocyte depot in the bone marrow, which is present under normal conditions, is smaller when the peripheral reticulocyte count is low, and the number of reticulocytes which can enter the circulation through the action of any brief stimulus is therefore smaller.

The results presented are much less striking than those reported by ERSLEV and coworkers, who produced a reticulocytosis of approximately three times the original level in healthy monkeys by injections of plasma from other monkeys rendered severely anemic by bleeding. Normal monkey plasma had no significant effect. However, plasma was injected daily for four consecutive days, the animals receiving 60–100 cc of plasma/kg, whereas these infants received only 2.6–6.7 cc/kg.

The humoral substances whose presence has been demonstrated are

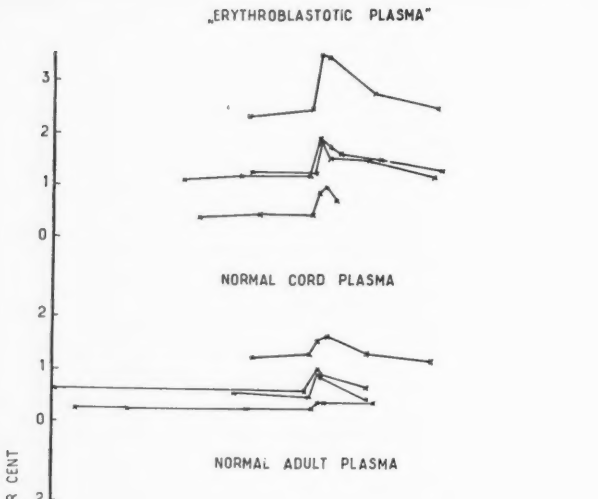

Fig. 1. Reticulocyte counts in small infants without blood disorders before and after i.v. injections of different kinds of plasma 15–20 cc.

perhaps produced in the liver, although their source is not definitely known. Certain clinical and experimental findings (SEIP 1953) seem to indicate the presence of an erythropoiesis-regulating center in the brain stem. The oxygen tension in this center probably governs the formation of these humoral factors, and thereby the rate of erythrocyte formation.

Summary

1. The existence of humoral reticulocytosis-producing factors in human plasma under certain conditions of intensive erythrocyte formation has been investigated by intravenous infusions given to small infants of (a) normal adult plasma, (b) plasma from the cord of normal newborns, and (c) plasma from infants with erythroblastosis.

2. Adult plasma produced no reticulocytosis.

3. Plasma from normal newborns and that from infants with erythroblastosis, both donor groups themselves showing a marked reticulocytosis, consistently produced a significant increase in the reticulocyte count in the recipient infants.

4. These findings extend the work of others on experimental animals and provide evidence for the existence of circulating reticulocytosis-producing substances controlling the rate of red cell formation in humans.

Existence de facteurs humoraux réglant la réticulocytose et l'érythropoïèse chez l'homme.

L'existence dans le plasma humain, de facteurs humoraux provoquant une réticulocytose, au cours des activations intenses de l'érythropoïèse, a été étudiée par l'injection intraveineuse à de jeunes nourrissons de: a) plasma adulte normal, b) plasma provenant du cordon de nouveaux-nés normaux, c) plasma d'enfants présentant une érythroblastose. Le plasma d'adultes ne provoquait aucune réticulocytose. Le plasma de nouveaux-nés normaux ou celui d'enfants en érythroblastose—deux groupes de donneurs montrant eux-mêmes une réticulocytose élevée—amenait un accroissement notable du taux de réticulocytes chez les récepteurs. Ces résultats confirment les travaux expérimentaux sur l'animal, et prouvent par conséquent l'existence de substances circulantes amenant une réticulocytose, et controlant le taux de formation des hématies chez l'homme.

Humorale Faktoren bei der Regulation des Retikulocytenspiegels und der Erythropoese beim Menschen.

Das Vorhandensein humoraler Retikulocyten-produzierender Faktoren im menschlichen Plasma wurde — unter bestimmten Umständen intensiver Erythrocytenbildung — durch intravenöse Injektion von kleinen Mengen (a) normalen Erwachsenenplasmas, (b) Plasma aus der Nabelschnur Neugeborener und (c) Plasma von Säuglingen mit Erythroblastose bei kleinen Säuglingen untersucht. Erwachsenenplasma ruft keine Retikulocytose hervor. Plasma von normalen Neugeborenen und solches von Säuglingen mit Erythroblastose, wobei beide Spendergruppen selbst eine deutliche Retikulocytose zeigen, haben übereinstimmend ein deutliches Ansteigen der Retikulocytenzahl beim Empfängersäugling zur Folge. Diese Befunde erweitern die tierexperimentellen Arbeiten anderer Autoren und bestärken die Wahrscheinlichkeit der Existenz zirkulierender, Retikulocyten-produzierender Substanzen, welche die Erythrocytenbildungsrate beim Menschen kontrollieren.

Factores humorales en la regulación del nivel reticulocitario y eritropoyesis en seres humanos.

Se investigo la existencia de factores humorales productores de reticulocitos en ciertas condiciones de intensiva formación eritrocitica:mediante la inyeccion intravenosa de: (a) plasma normal de adulto, (b) plasma del cordón de recién nacidos normales, (c) plasma de niños con eritroblastosis. El plasma de adultos no produjo respuesta reticulocitaria, el plasma de recién nacidos y de niños con eritroblastosis, ambos mostrando de por sí una tendencia a producir reticulocitos, produjeron en el receptor un significativo aumento del nivel reticulocitario.

References

Bert, P.: Sur la richesse en hémoglobine du sang des animaux vivant sur les haut lieux. Compt. rend. Acad. sc. *94*:805–807, 1882.

Carn[illegible]r, P. and Deflandre, C.: Sur l'activité hémopoïetique du sérum au cours de la régénération du sang. Compt. rend. Acad. sc. *143*:384–387, 1906.

Erslev, A.: Humoral regulation of red cell production. Blood *8*:349–357, 1953.

Erslev, A., Lavietes, P. H., and Van Wagenen, G.: Erythropoietic stimulation induced by 'anemic' serum. Proc. Soc. Exp. Biol. & Med. *83*:548–550, 1953.

Gra[illegible]W. C. and Root, W. S.: The relation of O2 in bone marrow blood to posthemorrhagic erythropoiesis. Am. J. Physiol. *150*:618–627, 1947.

HEILMEYER, L.: Zur Physiologie und Pathologie der Erythrocytenregulation. Verhandl. deutsch. Gesellsch. inn. Med. *45*:113–118, 1933.

HODGSON, G. and TOHA, J.: The erythropoietic effect of urine and plasma of repeatedly bled rabbits. Blood *9*:299–309, 1954.

MAGNUSSEN, J. D.: The influence of oxygen tension on the production of erythrocytes in vitro. Acta pharmacol. et toxicol. *5*:153–163, 1949.

MIESCHER, F.: Über die Beziehungen zwischen Meereshöhe und Beschaffenheit des Blutes. Correspondenz-Blatt f. schweiz. Ärzte. *23*:809–830, 1893.

SEIP, M.: Reticulocyte studies. Acta med. Scandinav. Suppl. *282*, 1953.

—: The reticulocyte level, and the erythrocyte production judged from reticulocyte studies, in newborn infants during the first week of life. Acta pædiat. *44*:000, 1955.

VIAULT, F.: Sur l'augmentation considérable du nombre des globules rouges dans le sang chez les habitants des hauts plateaux de l'Amérique du Sud. Compt. rend. Acad. sc. *111*:917–918, 1890.

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Welfare of Children, Stockholm.

Primary Enuresis

When is a child dry at night?

by GUNNAR KLACKENBERG

Introduction

The age at which a child gains control of his urinary bladder varies. As a rule, this occurs at an earlier stage by day than at night. Diurnal control is the final outcome of a complex interaction between involuntary and voluntary mechanisms. The primary functions of the bladder, which are not under the control of the will, are regulated by the autonomic nervous system. This is the dominant regulatory mechanism during infancy. At a certain threshold value of the distention of the bladder the sphincter relaxes, the tonus increases, the bladder is contracted and emptying takes place.

This threshold value for emptying varies considerably from one child to another and even for the same child under different conditions. During the child's development this basic function is regulated by the aid of cerebro-spinal impulses, first, probably, in the form of conditioned reflexes, and then gradually it is consciously directed as an expression of volition.

It is during these final stages of development towards complete control of the bladder that the training in cleanliness adopted by the mother may constitute either a positive or a negative factor: positive, in the sense that she can wisely adapt her measures in accordance with the signs of maturity that the child spontaneously displays; negative, when she is too ambitious in trying to get the child to be dry at an early stage, which often implies it is too early a stage. Premature training in cleanliness involves so many risks of provoking the adult to adopt an attitude towards the child, which may prove harmful to their relationship and possibly also to the development of the child's personality. It is better to avoid doing too much and to depend more on the spontaneous maturity of the normal child. In our rational age with its enthusiasm for cleanliness, the quite general use, for the last 7 or 8 years, of diaper pants in which cellulose wadding is inserted, has fortunately put a check on too zealous training.

In the nocturnal control of the bladder biological factors apparently play a still more important role than cultural influence. The ability of the bladder to retain, without emptying, the amount of urine received during the night, presupposes a high degree of neuro-muscular maturity. The delicate nervous interaction which takes place between the sphincters and the musculature of the walls of the bladder is probably not stimulated, to any great extent, by crude external means, such as, for example, waking the child for emptying the bladder. Also for theoretical reasons, training has a more restricted sphere of activity in respect to nocturnal control. Consequently, the time for this control should, as in the case of other biological functions which are principally concerned with maturative processes, display variations, and these times form a curve which is similar to that of other developmental processes.

Own Investigations

In order to study these conditions the author has taken his sample group from a Child Welfare Centre. When the mothers visit this centre, usually twice a year, they are in the habit of stating when their children stayed dry at night. It is not difficult to determine when this took place, as long as the problem is of current interest to the parents. As a rule, this ability does not develop from one night to another, but "failures" occur sporadically.

Children have been considered to be dry at night when 2–3 months have elapsed without the occurrence of wetting at night. If wetting at night began again after a longer interval than 2–3 months, then the time of the first dry period was taken. This apparently arbitrary determination is based, however, on the experience that a child who has gained control of his bladder for a period of 2–3 months after the beginning of a dry period does not lose this control, except as the result of some more or less manifest physical or mental influences. Isolated failures have not been taken into account.

As a rule, the children have been followed up to 6 years of age, and in this series those who are still bedwetters at night at this age, had been bedwetters practically continually during the whole of their past childhood. Accordingly, children are not included who have again begun to be wet after an interval of 2–3 months. Consequently, the investigation does not give any information about the frequency of nocturnal wetting, for example, at 6 years of age.

Result of the Study

The children are from a district in Stockholm (Lilla Essingen) where the great majority of the population belongs to social groups II and III. Altogether 315 children were investigated, 48.6 per cent boys and 51.4 per cent girls.

The girls were dry a little earlier than the boys, but the difference is so slight that, for the sake of clarity, the different curves have not been drawn separately.

As is shown in the graph, 7.9 per cent of the children were already dry at night at the age of one year. Sixty per cent had reached this stage when they were 2 years of age, and 87 per cent when they were 3 years old. At 6 years of age every 25th child has not yet gained control of its urinary bladder at night. The mothers frequently reported that other members of the family also suffered from the same symptoms until a more advanced age, in spite of the different forms of treatment that were tried. In this group of 5–6 year old bedwetters, who have wet their beds almost continually since birth, there may naturally also be children who, under more favourable environmental conditions, could have been dry earlier; but the tensions of emotional conflicts have been conducive to enuresis at a time when the children would otherwise have been mature enough to control their bladders at night.

In addition to enuresis, some of the children display neurotic traits, but here this investigation cannot presume to determine which is cause or effect. It should be possible to improve the situation of these children who are late in controlling their bladders at night. This may be done by curtailing the mother's conscious, too intense interest in nocturnal wetting and by giving the parents advice about removing the child's guilt feelings. Even if it is not possible to hasten spontaneous maturity in this way, we ought, at least, to be able to reduce the nervous effects on the child that a sense of guilt involves.

In his study of the functional development of children, WALLGREN has also made some observations on "nocturnal urinal continence". The children in his series, who were taken from a Child Welfare Centre in Gothenburg, were dry throughout the night at an earlier age, on an average when they were 16 months old. The deviations may perhaps be explained by differences in the samples investigated. Whereas the author endeavoured to include in his study all the children who went to the Child Welfare Centre to have their health checked during a certain number of years, WALLGREN has only taken into account "entirely normal children" whose mothers were interested and willing to take part in the investigation. The majority of Gothenburg children had no siblings and were all looked after by their mothers in their own homes.

The present investigation also afforded an insight into the training habits adopted in the homes. The information that the mothers were asked to give was principally about the time when training with a pot was started, i.e. the regular attempts on the part of the mothers to get the children to

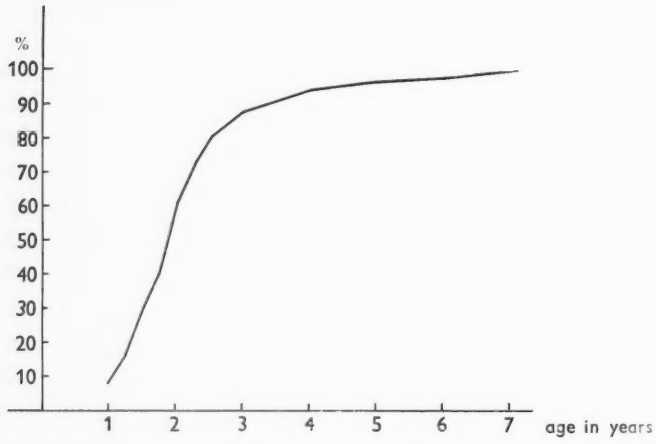

Fig. 1.

empty their bladders either by holding the child on a pot or by letting him sit on it. For obvious reasons the information is not as reliable as that referring to the time when the children ceased to be wet at night. The children belonged to the age groups born in 1944 and 1945. At that time, diaper pants in which cellulose wadding was inserted had not yet come into general use. It should be realised that this is one of the reasons that "training" began so early at that time. It was exceptional for mothers to wait until the child was 1 year old; in most cases "training" was started when the child was 6–7 months old. There was no correlation between the time "training" began and the cessation of nocturnal wetting. It may be worth noting that among those who were still bedwetters at 7 years of age were two whose mothers had regularly placed them on a pot when they were 3 months old; and on an average, those who had first become dry after 3 years had begun to be trained when they were 7 months old. To some extent, the practice of waking a child at night was adopted already at the age of 1 year. Among those persons who furnished any information about waking children at night, there were 50 who regularly attempted, in this way, to get the children dry at an early age, and 174 who left their children in peace. No information was available for the remainder of the subjects.

Discussion

The idea that a child is taught to be dry at night is widely held. Nocturnal control of urine is not, however, a training process but a maturing process. What may possibly be gained by waking and picking up a child in order to

hold him on a pot or to let him sit on it is either that the bed will be dry or the child will avoid having to lie for some hours in wet diapers. This may prove an advantage for children with sensitive skin or for those whose sleep is restless and who kick off their bedclothes.

For children who do not offer any resistance to being awakened, or who, after they have gratified the wishes of their parents, soon fall quietly asleep again, the procedure probably does not involve any disadvantage. The risk lies mainly in the expectations and demands for a quick result, which, in this respect, ambitious parents make on their children. However, with regard to children who do resist, who become tense and provoke coercion of different kinds or who subsequently lie awake for hours, there is every reason not to wake them. The refractory attitude or strain which results from the big fuss about the pot, may actually postpone the time when the bladder acquires the requisite degree of maturity. The same considerations may be presumed to apply to daytime training.

A less rigid and less coercive form of training, one that is more tolerant and better adapted to circumstances should, in the light of psychological experience, lessen the sense of guilt on account of enuresis. It ought to reduce refractoriness and aggressions and eliminate many of the problems which civilized man, on account of his foolish zeal, has created around a biological function that takes its natural course. In the sample which the author has worked on, there are children who, without the intervention of their parents, were dry before they were 1 year old; and at the same time there are also those who, despite regular "exemplary" training, continued to be bedwetters right up to the time they began to go to school.

Summary

A progressive study of children up to 7 years of age at a Child Welfare Centre shows that the time of cessation of "physiological" nocturnal wetting varies within wide limits. The nocturnal control of urine is not a result of training; no connection is discernible between it and either waking the child at night or training it in cleanliness at an early age.

L'énurésie primitive. Quand l'enfant devient-il propre, la nuit?

L'étude dans un centre de consultation d'enfants d'un groupe d'enfants agés au maximum de 7 ans, a révélé que l'âge auquel cessait l'énurésie nocturne habituelle, était essentiellement variable. Le contrôle nocturne du sphincter n'est pas le résultat d'une éducation. Il semble n'y avoir aucune relation avec le fait d'éveiller l'enfant la nuit ou de lui donner très tôt des habitudes de propreté.

Primäre Enuresis. Wann ist ein Kind nachts trocken?

Eine longitudinale Untersuchung von Kindern bis zu 7 Jahren in einer Fürsorgestelle zeigte, dass der Zeitpunkt der Beendigung des „physiologischen" Bettnässens in weiten

Grenzen variiert. Die nächtliche Urinkontrolle ist nicht ein Resultat des Trainings. Eine Beziehung mit dem Wecken des Kindes zur Nachtzeit oder mit einem Sauberkeits training im frühen Alter ist nicht zu erkennen.

Enuresis primaria. ¿ Cuando debe un niño dejar de mojarse por la noche ?

En un estudio longitudinal efectuado en niños hasta 7 años de edad se encontró que la época en que estos cesaban de mojar la cama varía dentro de amplios límites. El control nocturno de la orina no es el resultado de un aprendizaje. No se encontró ninguna relación entre éste y despertar al niño por la noche o enseñarle normas higiénicas desde edad temprana.

References

GESELL, A. *et al.*: The First Five Years of Life. Harper and Brothers Publishers, New York. 1940.
WALLGREN, A.: Functional development during infancy. Acta Paediat. *38:* 637, 1949.

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Prematurity and Pseudoprematurity

Studies of the developmental age in underweight newborns

by A.-L. BERGSTRÖM, M.-B. GUNTHER, I. OLOW and B. SÖDERLING

According to international stipulations a premature (immature) is defined as a newborn living child weighing 2,500 g or less. The definition is old (originating from the Geneva Commission of 1937), but as late as 1950 it was the subject of a discussion and decision by an expert committee in the WHO. Then it was agreed that the definition should remain unchanged, considering the fact that weight constitutes the only objective factor that could be used anywhere and, consequently, be applied to statistical comparisons.

However, one of the members of the committee, MARCEL LELONG, feeling conscious of the deficiencies of the definition, proposed some valuable points of view. The fact that only viable newborns were to be included among prematures would, in his opinion, upset statistics. He also emphasized that a bare statement of weight does not take into consideration the duration of the pregnancy, and is restricted to growth and state of nutrition. He pointed out four reasons why a child is underweight at birth, as follows: (1) Healthy children may be born prematurely and thus be immature in the real sense of the word. (2) Fully developed children may be underweight on account of some disease in progress or some disease during an earlier stage of the pregnancy in the children or the mothers. (3) There may be morbid immature children. (4) Fully developed healthy children may have low weights at birth conditioned by constitution or race. Finally, LELONG suggested that physiologic criteria of viability should be looked for rather than anthropometric and morphologic.

As early as 1919 YLLPÖ urged that, even in the case of fetuses, a differentiation should be made between long and short, thin and thick.

Certain changes in the appearance of the placenta (such as infarcts, etc.) have been proved to produce underweight fully developed children (SÖDERLING and others); likewise, for some reason or other, a kind of pressure on the umbilical cord (e.g., one or more twists around the neck), causing a de-

ficiency in the nutrition of the fetus. For such children whose low weight at birth is not to be explained by any general lack of viability (circulation, temperature-regulating capacity, nutrition) the term of intra-uterine undernutrition has been coined (SÖDERLING).

Since 1952, closer attention has been paid to the correlation between the low weight of so-called prematures, the degree of maturity and the general viability. To these studies, GESELL's scheme of the regular development of reflexes has been applied. The weight at birth often seems, in this connection, rather useless. The opinion of the woman concerned and the conclusions of the obstetricians regarding the duration of a pregnancy appear more dependable, even though, for well-known reasons, reliable information cannot always be expected even in this case. In the aforementioned work by GESELL, an account is given of extremely careful observations on 22 children born in the 6th to 8th month of pregnancy, the weights at birth varying from 800 to 2,100 g.

TABLE 1

Scheme quoted from GESELL's work.

1. Spontaneous supine behavior
2. Visual awareness: red ring / lamp
3. Manual grasp
4. Auditory awareness
5. Proprioceptive awareness
6. Functional laterality
7. Regard for face
8. Head station
9. Prone behavior
10. Muscle tone
11. Sleep-wake status

In the course of their investigations, the present authors have modified GESELL's original scheme (Table 1) in view of the fact that some of his tests have seemed too subjective and lacking in practical applicability in routine examinations. Accordingly, we have, among other things, excluded his test with the red ring and his estimate of the muscular tonus, as being in our opinion too subjective. The tonic-neck observations have also been excluded because a child may assume such a posture reflexly for a considerable period, viz., from the 28th fetal week up to 16 weeks after being fully developed. Thus, they provide no indication of time. As regards the value of the hearing test, we are as yet not inclined to express any opinion on account of the difficulty of securing a suitable test material. Also, the testing has only been applied in a few cases.

Table 2 shows the scheme we have gradually developed. A brief report of the test procedure will also be found there. The examinations in accordance with this scheme have been performed once a week until a child has reached its maximum degree of accomplishment. The examination should take place at an optimal time for the child.

TABLE 2

The present authors' scheme.

1. Visual perception (lamp)
   - − no reaction
   - + faint blink, slightly delayed
   - + + marked reaction

2. Moro's reflex
   Proprioceptive perception (striking with fist on table at a distance of 25–30 cm)
   - − no reaction
   - + faint reaction
   - + + marked reaction

3. Manual grasping (an earpick or the investigator's finger is slowly pressed against the palms of the hands)
   - − no reaction
   - + faint reaction
   - + + marked reaction

4. Prone behavior (child in prone position with head in sagittal plane, arms bent forward, legs outstretched)
   - + slight movement of head
   - + + turns head to either side, slight flexion of legs
   - + + + draws up legs under body

5. Swallowing reflex
   - − lacking
   - + noted

6. Sucking reflex
   - − lacking
   - + sucks only on tube
   - + + sucks also on teat

7. Sleeping-waking status
   - − short sleeping and waking periods alternate rapidly
   - + short but distinct waking periods and longer sleeping periods
   - + + waking periods of approx $\frac{1}{2}$–1 hour

8. Temperature-regulating capacity
   - − incubator or water-bottle, heating pad
   - + without extra warming

We have found an hour before a meal to be the most favorable since a child should be neither too hungry nor too satisfied. Often a child discloses sequelae of the delivery, such as being affected by the narcosis, symptoms of commotio, flexion posture of the legs after breech presentation, etc., because of which the first examination should be deferred to the second or third day of life. The result may be affected later by icterus. For this reason, the time of its appearance should be stated.

TABLE 3

Present authors' material, including 33 children classified according to weight and stated number of fetal weeks.

Fetal week	1,000–1,490 g	1,500–1,990 g	2,000–2,490 g
28–29	1	1	1
30–31			1
32–33		5	2
34–35		1	2
36–37		3	5
38–39		1	8
40–	1		1

Material

The present material comprises 33 children. In Table 3 they have been classified in three weight groups. In addition, the table includes the duration of the pregnancy, according to data given by the mothers.

Results

Tables 4 and 5 show the hospital case records of two children of approximately the same weight at birth, one born in the 29th, the other in the 36th fetal week. A comparison between the two case records shows clearly the different degrees of maturity. In addition to the routine test results, there are notes in the case records of the type of heat appliance, the manner of feeding, the weight of the child, the caloric intake, and complications in the newborn period, if any.

The present examinations show that the maximum of grasping and prone behavior reflexes of a child occur simultaneously with the capacity to suck *ad lib.*, accomplishments that appear in the 35th to 37th fetal week. According to our observations, this indicates a physiologic connection, implying, in the event of a lack of interplay between these factors, the presence of some disease or deformity in the child. It is also possible, by means of these accomplishments, to form a rather exact idea of the duration of a pregnancy and the degree of maturity of a child.

Also, by recording the signs of prematurity that were formerly used, such as woolen hair, growth of the nails, etc., we have been able to show that these signs do not agree with the standards of maturity defined by ourselves and that, accordingly, they cannot be adopted as criteria of the maturity or immaturity, respectively, of a child.

TABLE 4

Name: E.-M. A–n, Hospital Case Record Number 676/54, born 3/8 1954.

Last menstruation: 15/1 1954 Birth weight: 1,270 g
Fetal movements: end of May Length: 37 cm
Expected delivery: 23/10 1954.

Date of examination	9/8	23/8	6/9	22/9	11/10
Age: day of life	7	21	35	51	70
fetal week	29	31	33	35	38
Light reflex	+	+ +	+ +		
Moro's reflex	–	+	+	+ +	
Grasping reflex: carpick	–	–	+	+ +	
finger	–	–	+	+ +	
Prone behavior	+	+	+ +	+ + +	
Swallowing reflex	–	+	+		
Sucking reflex	–	+	+ +		
Waking state	–	+	+		
Temp.-regulating capacity	–	–	–	+ (28/9)	
Incubator	+	+	+	–	
Bed				+	
Oxygen	–	–	–		
Tube	+	+	+	–	
Teat	–	–	–	+ (15/9)	
Food *ad. lib.*	–	–	–	+	
Icterus					
"Commotio"					
Remark: 14/8 attacks of cyanosis with lethargy					
Weight, g	890	1,010	1,200	1,520	2,290
Total amount of calories	42	98	112	182	448
Cal/kg	47	97	93	120	196

The comprehensive literature regarding prematures is totally dominated by discussions of feeding and nursing. Questions of development are very seldom touched upon and nowhere have we been able to trace any work in which attention is paid to GESELL's aforementioned investigations. Several authors, however, reveal a critical attitude to the term prematurity, among them LELONG. Such physiologic criteria for an estimation of viability and degree of maturity in underweight newborns as he suggests, we have made an attempt to develop in a study of the reflexes and the ability to take nour-

TABLE 5

Name: A.-S. J–n. Hospital Case Record Number 637/54, born 19/7 1954.

Last menstruation: 8/11 1953 Birth weight: 1,560 g
Fetal movements:? Length: 44 cm
Expected delivery: 15/8 1954.

Date of examination	20/7	26/7	2/8	9/8	13/9
Age: Day of life	1	7	14	21	56
Fetal week	36	37	38	39	+ 4
Light reflex	+ +	+ +	+ +		
Moro's reflex	+ +	+ +	+ +		
Grasping reflex: earpick	+ +	+ +	+ +		
finger	+ +	+ +	+ +		
Prone behavior	0	+ + +	+ + +		
Swallowing reflex	+	+	+		
Sucking reflex	0	+ +	+ +		
Waking state	+	+	+ +		
Temp.-regulating capacity	−	−	+		
Incubator	+	+			
Bed			+		
Oxygen	−				
Tube	0				
Teat	0				
Food *ad lib.*		+	+		
Icterus	−	−	−		
"Commotio"	+	−	−		
Remark: Pentothal narcosis. Vomiting child from the start					
Weight g		1,390	1,530	1,750	2,849
Total amount of calories		161	212	349	551
Cal/kg		116	139	194	193

ishment in the underweight newborn. We feel that we have found an acceptable way to produce a more adequate classification. A classified material is bound to offer a basis for statistical and prognostic statements that are more satisfactory than those originating from the undifferentiated material compiled with reference to one single factor, viz., the weight at birth.

Summary

Studies of the connection between the reflexes and sucking ability of underweight children have been performed on the basis of GESELL's scheme in his work entitled *The Embryology of Behavior*. In the course of routine examinations, some of the "tests" carried out by GESELL were found to be too subjective or impracticable. Accordingly, they were eliminated from the definite examination scheme. The series includes 33 prematures with a weight at birth varying from 1,160 to 2,490 g. The examinations so far performed suggest that the maximum of grasping and prone behavior reflexes of the children appear simultaneously with the ability to suck *ad lib.* and, further, that these accomplishments occur in the 35th to 37th fetal week. Should this correlation later prove to be physiologic morbidity or deformity in the child should be suspected when there is a lack of simultaneity between these factors. In addition, it should be possible, on the basis of a child's accomplishments, to determine a fairly exact duration of the pregnancy. Finally, emphasis is laid on the advantages of physiologic criteria as a basis for judging prematurity, rather than the only method so far accepted, reliance on the weight at birth.

Prématurité et Pseudo-prématurité.

Cette étude porte sur le développement de 33 prématurés, dont le poids de naissance variait entre 1160 g et 2490 g. Les examens semblent indiquer que les reflexes de « grasping », et du comportement à plat ventre des enfants, apparaissent en même temps que la possiblité de sucer à volonté, et que ce développement survient au cours des 35 à 37 semaines foetales. Si l'on admet que cette corrélation soit physiologique, une absence de simultanéité dans l'apparition des deux facteurs devrait amener à suspecter quelque phénomène pathologique. De plus, la possibilité serait ainsi offerte de fixer une durée très précise de la grossesse, en se basant sur le développement de l'enfant. Enfin, sont soulignés les avantages d'un critère physiologique de prématurité, par opposition à la méthode habituelle basée sur le poids de naissance.

Prematurität und Pseudoprematurität.

Die Entwicklung von 33 frühgeborenen Säuglingen mit einem Geburtsgewicht zwischen 1160 und 2490 g wurde studiert. Die Untersuchung ergab, dass die Mehrzahl der Greif- und Lagereflexe der Kinder gleichzeitig mit der Fähigkeit zum Saugen auftreten, weiter, dass diese Fähigkeiten in der 35.–37. Fetalwoche erscheinen. Sollte diese Übereinstimmung sich als physiologisch erweisen, könnte beim Fehlen der Gleichzeitigkeit zwischen diesen beiden Faktoren Krankheit oder Deformität beim Kind vermutet werden. Zusätzlich könnte es möglich sein, auf Grund der Fähigkeiten des Kindes eine fast genaue Dauer der Schwangerschaft zu bestimmen. Schliesslich wird mit Nachdruck auf die Vorteile der physiologischen Kriterien als Beurteilungsgrundlage bei Frühgeborenen gegenüber der weitverbreiteten, auf das Geburtsgewicht abzielenden Methode hingewiesen.

Prematurez y Pseudoprematurez.

Se estudió el desarrollo de 33 prematuros cuyos pesos al nacer variaron entre 1160 y 2490 g. Los exámenes sugieron que el grasping reflex y los reflexos "pronos" aparecen

simultaneamente con la succión voluntaria entre la 35 y 37 semana de embarazo. Si está esta simultaneidad en la aparición de ambos reflejos es fisiológica, cualquier ruptura de esta relación debe ser sospechosa de malformación o morbilidad en el pequeño. Además, puede ser posible en base al comportamiento del niño, calcular con bastante exactitud la duración del embarazo. Se hace hincapié en la ventaja de usar un metodo fisiológico como base para juzgar la madurez, superior al único hasta ahora empleado, el del peso de nacimiento.

References

GESELL, A: The Embryology of Behavior. Harper & Brothers, New York, 1945.
LELONG, M.: Definition, critères et fréquence de la prematurité. Semaine des hôp. Paris *27:* 2937, 1951.
SÖDERLING, B.: Pseudoprematurity. Acta pædiat. *42:* 520, 1953.

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From the Infectious Diseases Hospital, Stockholm, Sweden

Long-Acting (DBED-) Penicillin

DBED- and Procaine-Pencillin in the Treatment of Scarlet Fever

A Clinical and Sero-bacteriological Follow-up Study

by JUSTUS STRÖM and GÖSTA TUNEVALL

In several previous studies on large groups of scarlet fever patients STRÖM (5, 6, 7, 8) noted the effect of different types of penicillin therapy. Thus, in patients treated parenterally with procaine-penicillin the number of bacteriological relapses was considerably lower than after oral treatment, indicating a more complete elimination of the streptococci by the former type of treatment (7). On the other hand, the development of immunity was markedly impaired by penicillin therapy and especially by treatment begun early (8). During the last few years, therefore, fresh and uncomplicated cases of scarlet fever have been treated orally, with the lowest dosage found to yield a good therapeutic result.

In our search for convenient penicillin therapy in scarlet fever, long-acting penicillin has now been employed. N,N^1-dibensylethylenediamin-*bis*-bensyl-penicillin (DBED-penicillin) or "Bicillin" is such a compound, now produced in Sweden (licence: Wyeth Institute) under the trade name of *Penditan*. In Penditan comp., procaine-penicillin has been added in order to combine protracted duration with a high initial concentration. In order to attain the highest possible degree of immunization we chose a low dosage comparable to the amount used by STOLLERMAN & RUSOFF and WANNAMAKER & coworkers for antirheumatic prophylaxis.

Material and Methods

All fresh and uncomplicated scarlet fever cases were divided at random among the following four series:

P_{d_2} = Penditan injected on the 2nd and the 15th day after admission.
P_{d_3} = Penditan injected on the 2nd, the 8th, and the 15th day.
P_{dco} = Penditan comp. injected on the 2nd, Penditan on the 8th and the 15th day
P_t = Procaine-penicillin tablets orally.

TABLE 1

Age years	Series P_{d2} & P_{d3} Penditan	Series P_{dco} [1] Penditan + Proc.-pen.		Series P_t Proc.-pen. (oral)
0	120,000	120,000	120,000	50,000 × 3
1–4	240,000	240,000	240,000	100,000 × 3
5–9	360,000	360,000	360,000	150,000 × 3
10–14	480,000	480,000	480,000	200,000 × 3
15–	600,000	600,000	600,000	250,000 × 3

[1] First injection; 2nd and 3rd injections as in series P_{d3}.

Each group contained slightly more than 100 patients.

The dosage schedules are shown in Table 1.

Swabs from nose, throat, impetiginous lesions, and vagina were cultivated for hemolytic streptococci daily (5 per cent horse blood-agar plates containing gentian violet $1:2 \times 10^6$). Determinations of the erythrocyte sedimentation rate (for children below five years of age a micro-method was used) and electrocardiograms were done every week during hospitalization and at two consecutive follow-up examinations. The antistreptolysin reaction was determined on admission and, in patients over five years, after two and five weeks. The hospitalization time was at least 15 days. For discharge three consecutive negative tests for streptococci were required. Follow-up examinations were performed one and three weeks after discharge.

Penicillin Concentrations in Serum

From about 10 children in each of the groups P_{d2}, P_{d3}, and P_{dco} blood samples were drawn one hour after the first Penditan injection and after 1, 7, 8, and 14 days, which means that, in the P_{d3} and P_{dco} groups, samples were drawn at the second injection and one day thereafter. The penicillin concentrations were determined by serial dilution of the serum in skimmed milk and by using L. Bulgaricus as the test organism (TUNEVALL). In the P_t group no determinations were performed, as the concentrations obtained by this type of penicillin treatment are well known from previous studies (DIDING & WALLMARK).

Results

The results of the penicillin determinations will be seen in Fig. 1.

The median concentrations were close to the values found by previous investigators (STOLLERMAN & RUSOFF). However, the dispersion was considerable and it is worth noting that fairly many values were very low. 0.01–0.02 IU per ml.

As to the tablet series, DIDING & WALLMARK observed, after single doses of 200,000 IU procaine-penicillin in adults, a mean concentration of 0.69 IU/ml after 1 hour and 0.03 after 4 hours. Thus, in the P_t group

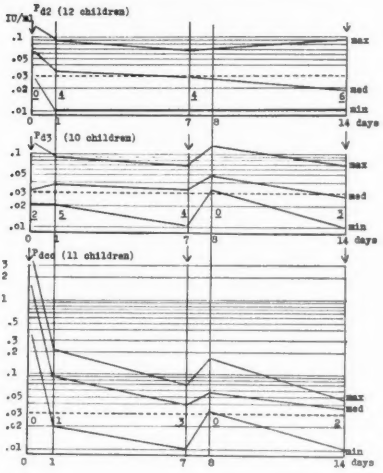

Fig. 1. Maximum, median, and minimum serum penicillin levels in groups P_{d2}, P_{d3}, and P_{dco}. Figures at the .02 line indicate numbers of values below .03 IU/ml.

TABLE 2

Effect on the streptococci.

Series	Disappearance of streptococci (mean, days)	Reappearance of streptococci (%)		
		During treatment	1 wk. after discharge	3 wk. after discharge
P_{d2}	2.1	15.7	2.0	4.0
P_{d3}	1.7	20.0	2.8	4.5
P_{dco}	1.7	18.2	4.5	9.0
P_t	2.0	13.0	8.2	9.1

the penicillin concentration is likely to have been higher than in the three Penditan groups during three 4-hour periods of the day. This condition may be more significant for the therapeutic effect than the fact that the concentration in the P_t group is likely to have been lower than in the Penditan groups during the rest of the day (EAGLE).

Thus, the P_t and the P_{dco} groups seem comparable in that the penicillin concentrations temporarily must have been far in excess of those necessary for bacteriostasis versus hemolytic streptococci. In the P_{d2} and P_{d3} groups the concentrations have ranged continuously just around those necessary for bacteriostasis.

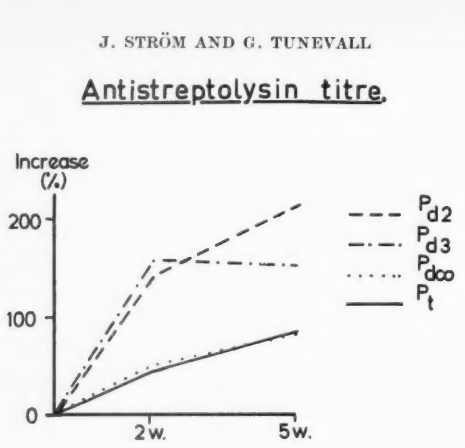

Fig. 2.

TABLE 3

Fever and sedimentation rate.

Series	Fever (days)	SR			MSR		
		On admiss.	After 1 wk.	After 2 wk.	On admiss.	After 1 wk.	After 2 wk.
P_{d2}	3.2	22.7	18.0	10.2	24.7	14.9	11.2
P_{d3}	3.1	26.6	18.0	11.1	26.6	17.6	12.4
P_{dco}	2.3	27.8	12.9	9.7	26.8	13.5	11.6
P_t	2.1	23.7	11.6	7.6	25.5	16.7	11.4

Bacteriological Results of Treatment

The rate of disappearance of hemolytic streptococci during treatment will be seen in Table 2. As a rule, negative cultures were obtained after two days. In two cases only in each of the groups P_{d_2} and P_{d_3} it was necessary to employ another penicillin compound in order to obtain negative cultures.

Table 2 also demonstrates that reappearance of streptococci during treatment occurred in 13–20 per cent of the cases, the lowest figure being found in the tablet series.

At the follow-up examinations, reappearance of streptococci occurred twice as often within the P_t and P_{dco} groups as in the P_{d_2} and P_{d_3} series. The difference, however, is not statistically proved.

In Fig. 2, the average antistreptolysin titre increases after two and five weeks are presented for the different groups, expressed in per cent of the initial value. It will be seen from the figure that the increase was con-

siderably higher in the P_{d_2} and P_{d_3} groups (with continuously low penicillin concentrations) than in the P_{dco} and P_t groups (with temporarily high penicillin concentrations). In the first two groups the average increases were 210 and 150 per cent respectively, in the latter groups 80 and 86 per cent respectively.

Clinical Results of Treatment

The duration of fever, as presented in Table 3, was shorter in the P_t and P_{dco} groups than in the P_{d_2} and P_{d_3} groups, this difference being statistically significant. As will be seen below, Penditan injections in some cases caused a rise of temperature. This rise, however, could hardly be responsible for the aforementioned difference, since the P_{dco} series belonged to the group in which the shorter duration of fever was found.

The sedimentation rate, also presented in Table 3, decreased more rapidly in the P_t and P_{dco} groups than in the others. The difference as to the rates after one week was significant for the $P_t + P_{dco}$ series versus the $P_{d_2} + P_{d_3}$ series; as to the rates after two weeks, only for the P_t group versus the $P_{d_2} + P_{d_3}$ group.

The complications occurring during an observation time of five weeks are reported in Table 4. On the whole, they have been fairly few and, above

TABLE 4

Complicated cases and complications.

(Observation time 5 weeks.)

Series	Pat. No.	Compl. cases		Complications							Second attacks (within 8 months)
		No.	%	Tonsillitis	Lymphadenit.	Otit.	Sinusitis	Impetigo	Myocarditis	Nephritis	
P_{d_2}	102	16	15.7	1	8	–	3	2	1	1	–
P_{d_3}	110	15	13.6	1	3	1	2	8	1	–	–
P_{dco}	110	16	14.5	2	7	–	–	7	–	–	3
P_t	100	13	13.0	2	8	–	1	3	–	2	1

all generally of no serious nature. Thus, counting only the more serious ones, otitis, sinusitis, myocarditis, and nephritis, 9 such complications occurred in the $P_{d_2} + P_{d_3}$ group versus 3 in the $P_t + P_{dco}$ group (4.2 versus 1.4 per cent). The P_{dco} group presented no such complications.

Second attacks of scarlet fever, on the other hand, occurred in four cases from the $P_t + P_{dco}$ group but in none from the others, the observation time being on an average 8 months.

Reactions Following Penditan Injections

On the site of injection, infiltration, reddening, and tenderness have occurred so as to cause discomfort in only 8 cases (about 1 per cent). Slight discomfort from local pains for a day or two has, however, been fairly common.

Exanthemas of the urticaria type have been observed in two cases.

A general reaction, fever, occasionally combined with tiredness and bad temper, has not been uncommon. On the first injection the temperature reaction was generally difficult to evaluate as, on that occasion, the temperature was still high. Nevertheless, an additional rise of temperature was observed in about 10 cases. In the same number of cases, already afebrile on admission, the temperature increased again following the injection.

At the second injection on the 8th day, the situation was more easily evaluated. In all, 220 such injections were given, with temperature rises (over 37.4°C) observed in 18 instances (8.2 per cent). Rises over 38°C occurred in only 6 cases (2.7 per cent). One patient reacted with fever on all three injections (38.5°, 38.6°, 38.0°, respectively). The temperature reaction was generally observed on the day after injection and was of short duration (1 day in 11 instances, 2 days in 4 instances, and 3 days in 3 instances).

Discussion

With respect to the penicillin concentrations found in serum, the P_{d_2} and P_{d_3} groups present similar conditions. In the former group the average concentration fell from slightly below 0.04 to 0.02 IU/ml during the course of two weeks, while, in the latter group, the second injection resulted in an increase up to 0.05 and a concentration after two weeks of 0.03 IU/ml. These values range just close to the minimum concentration necessary for bacteriostasis and they are not likely to afford very good conditions for the diffusion of penicillin in sufficient concentrations into possible sites of poor vascularization. Furthermore, therapeutically inadequate minimum concentrations were found fairly often which may account for the occasional poor results of treatment.

The $P_{d_{co}}$ group was very similar to the P_{d_3} group, with the exception of a period of high concentrations during the first day. Within the P_t group it is reasonable to count on periodically high concentrations during the whole course of treatment. The high levels thus obtained in the two last-mentioned groups may result in a bactericidal action as well as a possibility of diffusion of penicillin into "remote" sites of infection. Consequently it seems justifiable to discuss the P_{d_2} and P_{d_3} groups together as a low-level group and

the P_{dco} and P_t groups as a high-level group. As will be seen below, the therapeutic results confirm such a view.

Before discussing the clinical results it may be recalled that, in a previous study, STRÖM (7) found that the streptococci returned in a lower percentage during treatment in patients intensely treated with procaine-penicillin injections than in patients treated orally. This difference was likely to be due to a more complete elimination of the streptococci in the intensely treated group. In none of the groups now studied has the treatment been sufficient for such a complete elimination, as the present high-level group was comparable to the orally treated group of the previous investigation with respect to the penicillin concentrations in serum.

In the present material the rate of disappearance of the streptococci was nearly the same in all groups. However, reappearances found at the follow-up examination three weeks after discharge occurred twice as often in the high-level as in the low-level group, in spite of the probably somewhat more complete elimination of the streptococci in the former. This difference, though not significant statistically, may be compared with the observation of BJUGGREN & TUNEVALL of a correlation between deficient antibody formation on the one hand, and relapse rate on the other in pneumococcal otitis, and may thus suggest a less effective immunization in the high-level group. This suggestion was corroborated by a tendency towards lower antistreptolysin titre rises in the high-level group.

As to the clinical results, the high-level group displayed shorter duration of fever and fewer serious complications. Of four cases needing supplementary treatment all belonged to the low-level group. On the other hand, four second attacks of scarlet fever during the observation time of eight months all occurred in the high-level group, which conforms with the view expressed above of a less effective immunization following highly effective penicillin therapy, as well as with STRÖM's previous demonstration (8) of the interference of penicillin therapy with development of immunity.

Apparently, long-acting penicillin with the low dosage employed was not sufficient to control the appearance of complications, as was the treatment with combined long acting and procaine-penicillin. On the other hand, it is also evident that the more effective treatment interfered with the development of immunity.

It is noteworthy that Penditan injections were to some extent followed by local and general reactions. Though not serious, these reactions cannot be neglected. It may also be pointed out that the frequency of such reactions in this study was considerably higher than previously reported in connection with the use of DBED-penicillin in the antirheumatic prophylaxis.

Summary

Long-acting (DBED-) penicillin given in two doses two weeks apart or in three doses one week apart has not been sufficient in all cases to eliminate promtly the hemolytic streptococci or prevent the occurrence of serious complications. A significantly better effect was obtained by combining the first injection of long-acting penicillin with equal amounts of procaine-penicillin, or by continuous oral procaine-penicillin medication. The antistreptolysin titre increased more in the patients treated only with DBED-penicillin, which corresponded with the fact that late bacteriological relapses and second attacks of scarlet fever were less common in this group. Thus, highly effective penicillin therapy seems to be combined invariably with a poor acquisition of immunity.

The injections of DBED-penicillin were followed by marked local reactions in about 1 per cent and by temperature increases over 38° in 2.7 per cent of the cases.

Pénicilline-retard et Pénicilline-Procaine dans le traitement de la Scarlatine.

Des injections de Pénicilline-retard sur la base de deux injections à un intervalle de deux semaines, ou trois injections à un intervalle d'une semaine se sont révélées insuffisantes à éliminer rapidement le streptocoque hémolytique dans tous les cas, et à prévenir la survenue de complications. Un bien meilleur résultat a été obtenu en associant à la première injection de Pénicilline-retard, une dose égale de Pénicilline-Procaïne, ou en administrant cette dernière continuellement par voie orale. Le taux d'antistreptolysines a été plus élevé chez les malades traités uniquement par Pénicilline-retard. Dans ce groupe, les récidives bactériennes tardives, et les rechutes se sont montrées plus rares. Ainsi, une thérapeutique pénicillée très active semble s'accompagner d'une médiocre immunité acquise. Les injections de Pénicilline-retard ont été suivies de réactions locales importantes dans 1 % des cas, et d'une élévation thermique supérieure à 38° dans 2,7 % des cas.

Langwirkendes Penizillin und Procain-Penizillin in der Behandlung des Scharlachs.

Langwirkendes Penizillin, verabfolgt in 2 Dosen mit zweiwöchentlichem Abstand oder 3 Dosen mit wöchentlichem Abstand, ist für sich allein nicht ausreichend, in allen Fällen die hämolytischen Streptokokken zu eliminieren und das Auftreten ernsterer Komplikationen zu verhindern. Eine deutlich bessere Wirkung wurde durch Kombination der ersten Injektion eines langwirkenden Penizillins mit der gleichen Menge Procain-Penizillin erreicht, oder bei kontinuierlicher oraler Procain-Penizillin-Medikation. Der Antistreptolysintiter steigt bei Patienten, welche nur mit langwirkendem Penizillin behandelt wurden, mehr an; dieser Befund stimmt mit der Tatsache überein, dass späte bakteriologische Rezidive und Zweiterkrankungen an Scharlach in dieser Gruppe weniger häufig sind. Eine hochwirksame Penizillintherapie scheint unabdingbar mit einer schlechten Immunisierung kombiniert zu sein. Die Injektion langwirkenden Penizillins hatte bei 1 % der Fälle eine deutliche Lokalreaktion, bei 2,7 % einen Temperaturanstieg über 38° zur Folge.

Penicilina de acción lenta y penicilina procaína en el tratamiento de la escarlatina.

Dos dosis de penicilina lenta administradas con un intervalo de dos semanas, o tres dosis administradas con un intervalo de una semana, no fueron suficientes, en todos los casos, para eliminar rápidamente el estreptococo hemolítico ni prevenir complicaciones.

Un efecto significativamente mejor se obtuvo combinando una inyección de penicilina lenta con igual dosis de penicilina procaína o con esta última por vía oral continua. El título de antiestreptolisinas subió más en aquellos pacientes tratados solo con penicilina lenta lo cual coincide con el menor numero de recidivas bacteriológicas y nuevos ataques de la enfermedad. La alta efectividad de la terapía penicilínica parece estar invariablemente combinada con una pobre adquisición de inmunidad. Las inyecciones de penicilina retardada produjeron marcada reacción local en alrededor del 1 % y temperatura sobre 38° en 2,7 % de los casos.

References

1. Bjuggren, G. and Tunevall, G.: Otitis in childhood. Acta oto-laryng. *42:* 311, 1952.
2. Diding, N. and Wallmark, G.: Angående serumkoncentrationen vid peroral penicillinterapi. Svenska Läkartidn. *50:* 2495, 1953.
3. Eagle, H.: Speculation as to the thereapeutic significance of the penicillin blood level. Ann. Int. Med. *28:* 260, 1948.
4. Stollerman, Gene, H. and Rustoff, Jerome H.: Prophylaxis against group A streptococcal infections in rheumatic fever patients. J.A.M.A. *150:* 1571, 1952.
5. Ström, J.: Jämförande kliniska försök med penicillinbehandling per os och parenteralt vid scarlatina. Svenska Läkartidn. *47:* 1406, 1950.
6. —— Penicillin treatment of scarlet fever. Acta pædiat. *43:* 32, 1954.
7. —— Penicillin in the prevention of scarlet fever. Acta pædiat. *43:* 38, 1954.
8. —— Penicillin treatment and immunity to scarlatina. Acta pædiat. *43:* 267, 1954.
9. Tunevall, G.: Lactobacillus Bulgaricus as test organism in penicillin and streptomycin assays. Acta path. et microbiol. Scandinav. *26:* 720, 1949.
10. Wannamaker, Lewis W., Perry, William D., Eckhardt, George C., Denny, Floyd W., Rammelkamp, Charles H., Houser, Harold B. and Hahn, Edward, O.: The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state. New England J. Med. *249:* 1, 1953.

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Coeliac Disease. VI

A Rapid Method to Test Wheat Sensitivity

by H. A. WEIJERS and J. H. VAN DE KAMER

In previous experiments in coeliac patients, in addition to the subjective clinical observations, steatorrhoea was always used as an objective criterion to test the wheat sensitivity (1, 2).

As this steatorrhoea criterion involves lengthy experiments, efforts were made to determine the wheat sensitivity in another manner. Now if the deleterious effect were caused by the bound form of glutamine (3), it seemed quite possible that there would be an increase of blood glutamine content after oral administration of gliadin. In order to study this, a gliadin tolerance curve was made in coeliac patients. As controls we used the values in healthy children.

The fasting patient is given 350 mg gliadin per kg body weight by mouth, in 15–20 ml buttermilk. The blood glutamine content is determined according to the PRESCOTT-WAELSCH method on a micro scale in 0.3 ml plasma at zero, 1, 2, 3, 4 and 5 hours later (4, 5, 6).

The results are given in Table 1 and in Fig. 1, in which the mean glutamine contents of the blood of coeliac patients—15 with and 14 without wheat in their diets—and the mean values of 13 normal children are plotted.

It is obvious from these values that the blood glutamine level of coeliac patients increases considerably after receiving gliadin, whereas in normal children little change occurs.

It is also seen that the increase in blood glutamine of coeliac patients is on an average the same, whether or not their diet contains wheat.

It has been calculated that an increase of the blood glutamine content of more than 50 per cent is indicative of a sensitivity to wheat. Since none of the 14 normals showed an increase of more than 40 per cent, this conclusion is statistically sound.

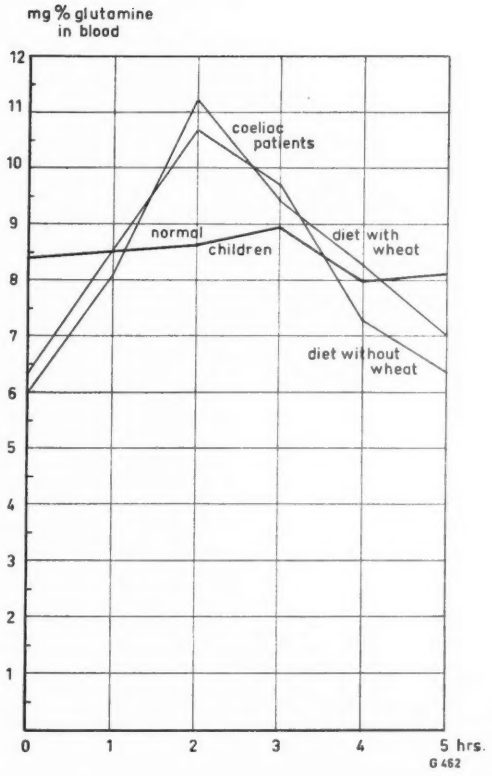

Fig. 1. Mean value of glutamine content of blood 1, 2, 3, 4 and 5 hrs after giving normal children and coeliac patients (on diets with and without wheat) 350 mg gliadin per kg body weight orally.

In 3 of our cases the wheat sensitivity was not accompanied by a rise of the blood glutamine level. However, after giving two of them 500 mg of gliadin per kg body weight the blood glutamine concentration increased by > 50 per cent too.

In our opinion the gliadin tolerance test can be used as a means to determine wheat sensitivity. It is especially valuable for testing out-patients. An investigation into the elevation of the blood glutamine level after oral feeding with deamidated gliadin, glutamine etc., is in progress.

TABLE 1

Glutamine content in mg % in the plasma of coeliac patients on diets with and without wheat and in the plasma of normal children after oral administration of gliadin (550 mg/kg body weight).

The gliadin was given after 12 hrs fasting; at this moment (= 0 hrs) the glutamine content of the blood was determined; the same was done after 1, 2, 3, 4 and 5 hrs, while the child kept fasting.

Coeliac patients on a diet containing wheat	Hours						Max. increase in % of the fasting value
	0	1	2	3	4	5	
P. K.	6.1	10.4	17.9	14.1	10.4	9.5	193
P. K.	4.8	5 9	14.0	10.5	9.1	5.3	192
W. K.	5.5	6.9	13.9	10.3	8.5	7.2	153
W. K.	4.1	7.5	6.4	6.0	5.5	4.2	83
T. T.	6.7	6.7	12.5	17.2	18.4	14.8	175
W. L.	3.8	7.9	6.6	5.4	5.0	4.2	108
M. H.	3.2	6.5	5.6	3.9	3.2	3.2	103
A. K.	7.7	8.6	14.0	11.1	10.2	7.9	82
A. H.	4.8	6.4	7.1	8.8	7.7	5.5	83
J. H.	4.8	5.6	8.6	6.6	4.8	3 7	79
M. S.	5.9	7.7	10.4	6.6	5.9	5.9	76
L. V.	9.0	12.5	14.5	12.0	9.8	9.3	61
C. U.	6.6	8.8	10.2	8.4	7.5	6.6	55
C. H.	5.5	6.8	8.7	6.6	5.5	6.2	58
H. U.	11.5	12.9	18.3	13.4	12.4	11.5	60
mean	6.0	8.1	11.2	9.4	8.3	7.0	104
Coeliac patients on a diet without wheat							
L. D.	3.6	3.6	5.7	5.0	3.6	3.6	58
L. D.	2.0	2.7	7.0	4.8	2.7	3.2	250[1]
G. B.	5.6	9.5	10.9	8.8	7.9	4.9	95
G. B.	7.5	10.7	12.9	9.6	7.5	6.8	72
G. B.	11.5	10.3	13.4	20.3	10.9	10.3	77
J. S.	8.3	13.9	14.9	12.7	10.8	10.0	79
J. S.	7.2	10.3	11.5	10.0	7.7	6.3	60
A. S.	7.9	9.6	9.0	8.2	8.5	8.0	22
A. S.	5.4	7.9	10.4	7.9	6.3	4.7	92[1]
J. B.	6.4	9.5	14.1	12.5	9.5	8.5	120
T. T.	4.3	6.7	9.5	5.7	3.7	3.7	121
A. J.	7.0	10.7	12.6	9.7	7.8	7.0	80
C. H.	6.6	7.1	10.6	14.4	10.6	7.1	118
P. K.	5.6	7.1	7.1	6.1	4.3	4.7	27
mean	6.4	8.5	10.7	9.7	7.3	6.3	91

[1] After administration of 500 mg gliadin per kg body weight.

Normal children	Hours						Max. increase in % of the fasting value
	0	1	2	3	4	5	
V. D.	9.1	11.6	11.6	12.7	10.5	10.1	40
A. N.	9.2	9.1	12.0	12.5	9.7	9.7	36
N. N.	6.4	7.6	7.1	8.1	7.6	7.6	27
G. N.	7.5	7.3	9.4	8.5	8.0	8.0	25
H. G.	7.2	7.5	8.0	8.9	8.0	7.2	24
J. B.	11.6	14.4	12.1	13.3	12.4	12.7	24
P. L.	8.3	7.2	8.8	7.2	5.7	7.7	6
A. F.	11.1	11.6	10.4	9.5	4.9	6.7	5
A. M.	11.2	12.8	9.6	10.1	11.1	10.1	14
I. N.	7.3	5.9	6.3	7.3	7.9	7.9	8
N. M.	4.5	3.7	4.2	3.7	3.7	4.2	−7
V. S.	6.3	5.8	5.0	6.3	6.7	5.8	6
J. R.	9.5	6.0	7.3	8.3	7.7	7.7	−13
mean	8.4	8.5	8.6	9.0	8.0	8.1	15

Summary

To test wheat sensitivity in coeliac patients, gliadin is given orally and the blood glutamine is determined. An increase of more than 50 per cent above the fasting level is indicative of sensitivity to wheat.

Maladie cœliaque : VI. *Une méthode rapide pour rechercher la sensibilité au froment.*

Pour déterminer la sensibilité au froment chez des patients atteints de maladie cœliaque, on donne de la gliadine par voie orale et on dose la glutamine dans le sang. Une augmentation de plus de 50 % au-dessus du taux à jeun indique une sensibilité au froment.

Coeliakie. VI. Eine Schnellmethode zur Feststellung von Weizenüberempfindlichkeit.

Um Weizenüberempfindlichkeit bei Coeliakie-Patienten zu testen, ist Gliadin per os gegeben und der Gehalt an Blut-Glutamin bestimmt worden. Ein Anstieg auf mehr als 50 % über den Nüchternwert zeigt eine Überempfindlichkeit gegen Weizen an.

Enfermedad celíaca. VI. Método rápido para medir la sensibilidad al trigo.

Para medir la sensibilidad al trigo en pacientes celíacos se administró gliadina por vía oral y se midió el nivel sanguíneo de glutamina. Un aumento sobre el 50 % del nivel de ayuno es indicativo de sensibilidad al trigo.

References

1. Dicke, W. K., Weijers, H. A. and Kamer, J. H. van de: Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. Acta pædiat. *42:* 34, 1953.
2. Kamer, J. H. van de, Weijers, H. A. and Dicke, W. K.: Coeliac disease. IV. An investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease. Acta pædiat. *42:* 223, 1953.

3. Kamer, J. H. van de and Weijers, H. A.: Coeliac disease. V. Some experiments on the cause of the harmful effect of wheat gliadin. (Preliminary communication.) Acta pædiat. *44:*465, 1955.
4. Prescott, Bl. A. and Waelsch, H.: A microdetermination of glutamic acid and its application to protein analysis. J. Biol. Chem. *164:* 331, 1946.
5. Prescott, Bl. A. and Waelsch, H.: Free and combined glutamic acid in human blood plasma and serum. J. Biol. Chem. *167:* 855, 1947.
6. Bessman, S. P., Magnes, J., Schwerin, P. and Waelsch, H.: The absorption of glutamic acid and glutamine. J. Biol. Chem. *175:* 817, 1948.

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Incidence of Atypical Mononuclear Cells in the Peripheral Blood of Children

by K. E. FICHTELIUS and B. VAHLQUIST

The mononuclear blood cells are traditionally classified as lymphocytes, monocytes, and plasma cells. Other, atypical mononuclear cells are also present in healthy subjects, and are especially numerous and pleomorphic in children. It is therefore very difficult to assess from this point of view whether or not a smear from a child is normal. The standard textbooks of haematology leave us uninformed on this point, and many actually give misleading information. Adequate data are available on the granulocyte, lymphocyte and monocyte counts at various ages, the most recent review of the relevant literature having been published by OPITZ and WEICKER, but nothing appears to have been written on the incidence of atypical mononuclear cells in the peripheral blood of children.

Abnormal, i.e. atypical, lymphocytes have been described in a number of pathological conditions. DOWNEY and MCKINLEY were the first to draw attention to the occurrence of these cells in infectious mononucleosis. Atypical lymphocytes have since been associated mainly with this disease, being termed "infectious mononucleosis cells", although the same type of cells has later been demonstrated in several other conditions, chiefly of viral aetiology. LITWINS and LEIBOWITZ proposed the term *virocytes* for these abnormal lymphocytes. This term has quite correctly been criticized, however, since similar abnormal lymphocytes have been shown to be present in conditions other than viral infections. Thus BEYREDER and HERZOG pointed out that atypical lymphocytes, which they called *small reaction forms*, are present in normal adults in numbers of not more than 4 per 100 lymphocytes; that they are present in increased numbers in bacterial infections as well as those due to viruses; and that they are also increased in malaria. They claim that at a certain phase acute inflammatory processes, with rise in temperature, show lymphatic reactions of largely similar type, the degree of reaction varying considerably according to the aetiological

agent. This lymphatic reaction takes place at roughly the same time as the neutrophil granulocytosis (the "neutrophil battle phase", cf. SCHILLING).

DOUGHERTY and FRANK examined the quantitative and qualitative changes in lymphocytes among stressed intact and adrenalectomized mice. They found that two types of lymphocytes are normally present in the blood, ordinary lymphocytes and large mononuclear cells with increased amounts of weakly basophil cytoplasm most closely comparable with Downey's type-II lymphocytes (cf. DOWNEY and STASNEY). DOUGHERTY and FRANK give this latter type of lymphocyte the term *stress lymphocyte*, since it is present in increased numbers among stressed animals. In a later work FRANK and DOUGHERTY apply their observations to man. The changes in the blood lymphocytes among healthy subjects were examined after administration of ACTH and adrenalin. They found a large number of lymphocytes which they judged to be morphologically identical with Downey's type-II lymphocytes (Ratio type II/normal lymphocytes = 0.36). They also found that type-II lymphocytes appeared to be less susceptible to the lytic effects of adrenocortical hormone than normal lymphocytes, and that type-II lymphocytes are produced by a nonadrenocortically mediated response to stress.

A variety of different definitions of atypical lymphocytes is to be found in the literature. Thus both the stress lymphocyte of Dougherty and Frank, and Downey's type-II cells, have a large amount of weakly basophil "hyaline" cytoplasm, whereas the cytoplasm of the reaction form of Beyreder and Herzog shows intense basophilia. The incidence of stress lymphocytes and of these "reaction forms" in normal blood was also quite different.

To avoid the difficulty of defining and adequately describing the atypical lymphocytes to be estimated, all mononuclear cells which cannot be referred to the groups *typical lymphocytes*, *monocytes*, and *plasma cells* may be grouped together as *atypical mononuclear cells*. The difficult distinction between typical and atypical lymphocytes, and between atypical lymphocytes and monocytes, indeed remains, but it should now be simpler to check the finding of others and make oneself understood. We have applied this classification *per viam exclusionem* in the present investigation. A short description of the morphology of typical lymphocytes, monocytes, and plasma cells is therefore given.

Typical lymphocytes.—The magnitude is 9–12 μ. The nucleus is round, stains deeply and is composed of dense aggregates of chromatin. No nucleoli are to be seen, if the cell has not been damaged. The cytoplasm is sky-blue and contains in some cells azurophil granules.

Typical monocytes.—In thin smears the monocyte is the largest cell in the blood, 16–22 μ. The nucleus is usually reniform or horseshoe-shaped, and the chromatin has

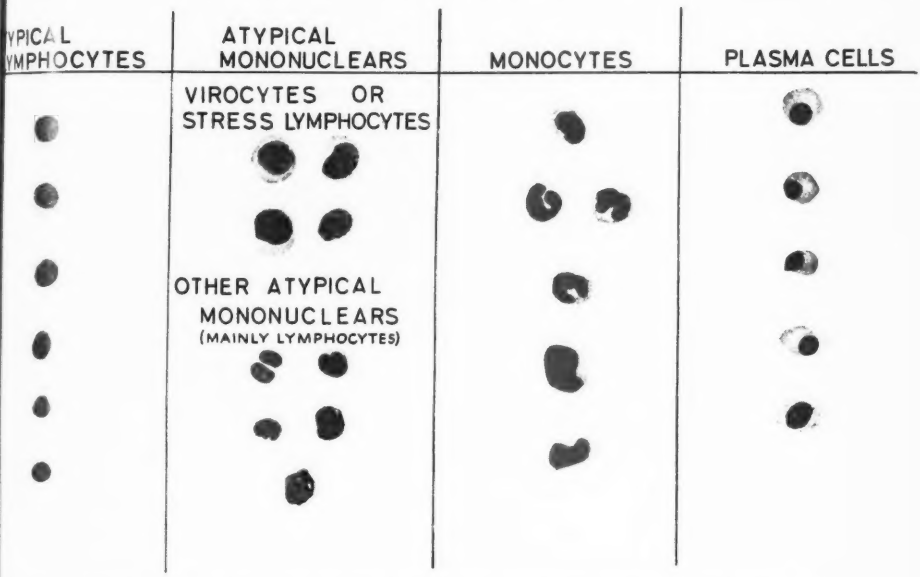

Fig. 1. Classification of the mononuclear cells. (The individual blood cells are reproduced from *Hämatologische Tafeln*, Sandoz, UNDRITZ.)

a fine, skein-like or lacy structure. No nucleoli are to be seen. The cytoplasm is greyish-blue and is sometimes filled with very fine azurophilic granules.

Typical plasma cells.—Diameter 14–20 μ. The nucleus is eccentrically placed and rather small, containing large dense masses of chromatin arranged in a wheel-spoke fashion ("Radkern"). In general no nucleoli are to be seen. The cytoplasm is intensely blue, sometimes with a little strain of red. There is usually a well-defined clear zone beside the nucleus (*archoplasma*).

Atypical mononuclear cells.—This group includes all mononuclear cells which cannot be placed in any of the above groups. From a morphological point of view some of these may be said to lie between the lymphocyte and the monocyte (Downey's type II, monocytoid lymphocytes, etc.), others resembling both the lymphocyte and the plasma cell (lymphatic plasma cells). It should be noted that this group includes cells with typical lymphocyte nuclei and vacuolated cytoplasm, whereas cells with typical lymphocyte nuclei without visible surrounding cytoplasm are classed with the typical lymphocytes.

The above classification is illustrated further by Fig. 1.

Material

Blood from 120 subjects has been examined, 40 from each of three age-groups.

I 1–3 years (day-nursery children).
II About 7 years (school-children).
III About 21 years (pupil nurses).

Each age-group is subdivided into two equal groups, one in Uppsala and one in Norrköping. The reason for this is that when the investigation was planned it was thought at the Paediatric Clinic in Uppsala that the incidence of atypical mononuclear cells in the peripheral blood of local children was unusually high, and it was therefore deemed advisable to make a comparison with the blood of the children in another town of similar size and type. The two towns are situated about 300 km apart, both very close to sea-level. All blood samples were taken in December 1952 or January 1953, and, to eliminate any possible seasonal or other variation in connexion with the date the Uppsala school-children were examined once again, in September 1953.

The tests performed included a total white-cell count and a differential count of 200 cells. In Groups I and II the samples were taken in the morning, and in Group III in the afternoon. All differential counts were done by the same laboratory technician, greatly experienced in haematology. She knew nothing of the purpose of the investigation or of the numbering of the slides. The smears were made by a second technician. The sedimentation rate was determined in all subjects.

Results

The various subgroups are compared in Table 1. The presence of atypical mononuclears in considerable number is a consistent feature in all groups, but their frequency varies from 409 ± 53 to $1{,}550 \pm 320$ pr cmm. The highest values are found in the two youngest age groups, but only for the Uppsala children is this difference against the oldest age group of statistical significance $0{,}001 < P < 0{,}01$ for the 1–3 year old, and $0{,}01 < P < 0{,}02$ for the 7 year old). The difference between the Uppsala and the Norrköping children, with higher values in the first-mentioned region, is in both age groups statistically significant ($0{,}001 < P < 0{,}01$).

Discussion

The leucocyte picture is determined by two principal groups of factors.

(1) Stress-producing agents of various kinds. These exercise a specific action, and in addition produce varying degrees of non-specific stereotypical stress reaction.

(2) "Conditioning factors" (SELYE), some of which are external (diet, temperature, light, etc.) and others internal (heredity, constitution, previous exposure, etc.).

There is no reason to suppose that the difference found between the children in the two towns should be due to "conditioning factors". The towns provide closely similar environments, and the living conditions of the subjects of the experiment are directly comparable. The cause must therefore

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TABLE I

The peripheral leucocyte picture at different ages in Uppsala and Norrköping ($M \pm \varepsilon_M$). The per cent figures are given in italics.

	I		II		III		II	
	Uppsala	Norrköping	Uppsala	Norrköping	Uppsala	Norrköping	Uppsala Jan. 53	Uppsala Sept. 53
Number of individuals in each group	20	20	20	20	21	19	20	18
Total leucocyte count per cmm	9665	7770	5085	6345	6100	6063	5085	6311
Non-segmented neutrophils per cmm	96 ± 29 *1.0*	66 ± 15 *0.9*	28 ± 8 *0.6*	47 ± 12 *0.8*	96 ± 28 *1.5*	45 ± 11 *0.8*	28 ± 8 *0.6*	115 ± 36 *2.2*
Segmented neutrophils per cmm	3747 ± 416 *38.3*	2976 ± 167 *38 6*	2282 ± 260 *44.0*	3024 ± 286 *48.2*	3857 ± 231 *62.8*	3869 ± 256 *63.1*	2282 ± 260 *44.0*	3184 ± 418 *50.4*
Eosinophils per cmm	359 ± 82 *3.4*	272 ± 42 *3.6*	191 ± 38 *3.8*	183 ± 26 *3.3*	103 ± 12 *1.7*	109 ± 24 *7.8*	191 ± 38 *3.8*	154 ± 26 *2.4*
Basophils per cmm	18 ± 7 *0.2*	12 ± 4 *0.2*	23 ± 7 *0.5*	17 ± 6 *0.3*	29 ± 11 *0.5*	12 ± 6 *0.2*	23 ± 7 *0.5*	22 ± 6 *0.4*
Typical lymphocytes per cmm	3407 ± 282 *36.4*	3345 ± 283 *42.2*	1353 ± 144 *27.1*	1770 ± 133 *30.7*	1147 ± 68 *19.1*	1222 ± 103 *20.4*	1353 ± 144 *27.1*	1646 ± 168 *25.4*
Atypical mononuclears per cmm	1550 ± 320 *14.2*	586 ± 77 *7.8*	906 ± 104 *17.3*	494 ± 73 *9.7*	581 ± 72 *9.1*	409 ± 53 *6.9*	906 ± 104 *17.3*	789 ± 84 *12.5*
Monocytes per cmm	541 ± 65 *5.7*	482 ± 44 *6.5*	333 ± 41 *6.5*	285 ± 36 *4.9*	333 ± 25 *5.8*	401 ± 33 *6.8*	333 ± 41 *6.5*	372 ± 31 *6.3*
Plasma cells per cmm	81 *0.8*	32 *0.4*	14 *0.3*	25 *0.5*	8 *0.1*	10 *0.2*	14 *0.3*	23 *0.4*
Sedimentation rate (micro-method) mm/hour	18	17	11	12	15	16	11	12

TABLE 2

The number of atypical mononuclear cells per cmm ($M \pm 2\sigma$)

	Uppsala	Norrköping
Group I	1550 ± 2858	586 ± 688
Group II	906 ± 932	494 ± 649
Group III	333 ± 230	409 ± 462

be sought in differences among factors inherent in Group 1. The similarity in the environments probably excludes differences in the degree of social stress. A possible cause would be in the influence of an infective agent. Perhaps the most obvious explanation would be some subclinical infection current in Uppsala at the time of the investigation. There is, however, no difference between the sedimentation rate in the groups compared and there seems to be no connexion between this reaction and the number of atypical mononuclears in the blood.

The leucocyte picture in the Uppsala children must be interpreted as pathological compared with that in Norrköping, but it is not certain whether the Norrköping values are normal—comparison with the blood picture of the children in a third region might reveal another state of affairs. The investigation described clearly cannot solve the problem of how many atypical mononuclear cells are normally present in infection-free Swedish children in the age-groups in question, but it can give some idea of the blood-picture among *apparently* healthy individuals. The likely limits of the atypical mononuclear cell count are given in Table 2. (The calculation has been done without respect to skewness of distribution.)

Summary

The presence of atypical mononuclear cells in the peripheral blood is a regular feature in all age groups examined, 1–3, 7 and 21 yrs. The frequency of these cells is highest in the youngest age groups, but only in one of the two investigation areas is this difference of statistical significance. The individual variation is great and the demarcation between normal and pathological is never well defined. Subclinical infections are probably of importance in this connection.

The authors wish to express their sincere thanks to Dr. E. UNDRITZ, Basel, for valuable suggestions and to Mrs. EDITH JACOBS for meticulous work in examining the blood.

Présence de cellules mononucléaires atypiques dans le sang périphérique chez l'enfant.

La présence de cellules mononucléaires atypiques dans le sang périphérique est un phénomène régulier à l'examen de tous les groupes étudiés — 1–3, 7 et 21 ans. La fréquence avec laquelle on rencontre ces cellules est la plus élevée dans le groupe le plus jeune. Mais c'est seulement dans une des deux séries de recherche que cette différence acquiert une importance statistique. Les variations individuelles, probablement en rapport avec des infections infracliniques, sont importantes et rendent difficile la démarcation entre le normal et le pathologique.

Über das Vorkommen von atypischen Monocyten im peripheren Blut bei Kindern.

Das Vorkommen von atypischen Monocyten im peripheren Blut ist bei allen untersuchten Altersgruppen, 1–3, 7 und 21 Jahre, eine regelmässige Erscheinung. Die Häufigkeit dieser Zellen ist in den jüngsten Altersgruppen am höchsten, aber nur in einer der zwei Untersuchungsreihen ist diese Differenz von statistischer Bedeutung. Die individuelle Schwankungsbreite ist gross und die Abgrenzung zwischen normal und pathologisch ist nie gut bestimmbar. Subklinische Infektionen sind in diesem Zusammenhang wahrscheinlich von Bedeutung.

Incidencia de células mononucleadas atípicas en la sangre periférica.

En todos los grupos estudiados, de 1–3, 7 y 21 años, la presencia de células mononucleadas atípicas en la sangre periférica fué un hallazgo regular. Su frecuencia fué mas alta en los grupos mas jóvenes, pero solo en una de las dos áreas de investigación esta diferencia mostró ser de significación estadística. La variación es grande y los límites entre normal y patológico nunca bien definidos, hechos que pueden ser atribuidos a infecciones subclínicas.

References

Beyreder, J. and Herzog, E.: Die lymphatische Reaktion als allgemeines Symptom akuter Erkrankungen. Wien. Z. inn. Med. *34:* 66, 1953.

Dougherty, T. F. and Frank, J. A.: The quantitative and qualitative responses of blood lymphocytes to stress stimuli. J. Lab. Clin. Med. *42:* 530, 1953.

Downey, H. and McKinlay, C. A.: Acute lymphadenosis compared with acute lymphatic leukemia. Arch. int. Med. *32:* 82, 1923.

Downey, H. and Stasney, J.: Infectious mononucleosis, Part II. Hematologic studies. J. Amer. Med. Ass. *105:* 764, 1935.

Frank, J. A. and Dougherty, T. F.: The assessment of stress in human subjects by means of quantitative and qualitative changes of blood lymphocytes. J. Lab. Clin. Med. *42:* 538, 1953.

Litwins, J. and Leibowitz, S.: Abnormal lymphocytes ("virocytes") in virus diseases other than infectious mononucleosis. Acta haemat. *5:* 223, 1951.

Opitz, H. and Weicker, H.: Das Blut, *in* Biologische Daten für den Kinderarzt. Berlin: Springer Verlag 1954.

Schilling, V.: Das Blutbild, 10. Aufl. Jena: Gustav Fischer 1933.

Selye, H.: Stress: experimental background and clinical application. Triangle, The Sandoz J. Med. Sc. *1:* 214, 1954.

Unschitz, E.: Hämatologische Tafeln. Sandoz A.G., Basel. 1952.

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A Comparative Study on the Mode of Action of Dihydrotachysterol and Vitamin D on the Calcium Metabolism

by ARVID CARLSSON and BERTIL LINDQUIST[1]

Besides vitamin D and the parathyroid hormone, dihydrotachysterol is known to have a marked influence on the metabolism of Ca and P. This substance is generally said to have a specific effect in increasing the concentration of Ca in the blood and in relieving the symptoms of parathyroid insufficiency. ALBRIGHT and coworkers (ALBRIGHT, BLOOMBERG, DRAKE and SULKOWITCH; ALBRIGHT, SULKOWITCH and BLOOMBERG; cf. ALBRIGHT and REIFENSTEIN) reported a clinical study comparing the effect of vitamin D, the parathyroid hormone and dihydrotachysterol on Ca and P metabolism in rickets and idiopathic hypoparathyroidism. The authors found that dihydrotachysterol, like vitamin D, increased the intestinal absorption of Ca and the excretion of P in the urine. Dihydrotachysterol had, however, more "phosphorus-excretion-effect per unit of calcium-absorption-effect" than vitamin D. Since the main action of the parathyroid hormone, according to their view, was to increase P excretion in the urine, they therefore concluded that the action of dihydrotachysterol more closely resembled that of the hormone than did the action of vitamin D. The possibility exists, however, that the differences observed between vitamin D and dihydrotachysterol in their investigation were referable to dosage rather than to qualitative differences. Further, no consideration was given to the possibility of a direct effect on the bones. Instead, the opinion of ALBRIGHT and coworkers is that the excretion of P by the kidney brings about a decrease in the serum P level; this tends to make the serum less saturated with respect to the bone salt and will then result in an increased mobilization of Ca from the bones.

In experiments on rats SHOHL, FAN and FARBER interpreted their results as being in agreement with the hypothesis presented by ALBRIGHT *et al.* They found that dihydrotachysterol was more effective in the cure of rickets

[1] With the technical assistance of J. Liljekvist and K. Rosengren.

when the P intake was high and the Ca intake low than vice versa. Their findings were, however, based mainly on histologic methods, and there seemed to be certain difficulties concerning interpretation. In a later paper SHOHL and FARBER clearly demonstrated that dihydrotachysterol was capable of curing rickets in rats; the dosage required was, however, much higher than the corresponding dosage of vitamin D, and the therapeutic range was much narrower.

CORRELL and WISE demonstrated an antirachitic effect of dihydrotachysterol in rats and chickens. In chickens dihydrotachysterol was more effective than calciferol, indicating that the antirachitic action of the former compound is not due to contamination by the latter compound. They also showed a decrease in serum phosphatase activity in chickens after the administration of dihydrotachysterol. They considered that the action of dihydrotachysterol resembled that of vitamin D rather than that of the parathyroid hormone.

By means of histological technique LATTA and TRISTAN studied the nature of changes occurring in growing bone resulting from toxic dosage of dihydrotachysterol. They found abundant evidence of bone resorption, especially in the compact bone of the shafts. The authors supposed that similar changes seen after administration of massive doses of vitamin D may be caused by a contamination with dihydrotachysterol.

MCLEAN studied the action of dihydrotachysterol and calciferol on rats, and he also presented an excellent review of the earlier literature. He distinguished between the "antirachitic activity" and the "calcemic principle", which he regarded as identical with the property that, in sufficiently large doses, leads to toxic symptoms. MCLEAN believed that the calcemic effects of dihydrotachysterol and calciferol were similar, if not identical, and were primarily caused by "the continuous influence of these substances on the interchange of calcium between plasma and bone, resulting in an increased mobilization of bone salt". Further, he was of the opinion that "the characteristics of the sterol molecule responsible for its antirachitic activity are not those responsible for the toxic effects".

In earlier papers we have presented evidence to show that vitamin D even in "physiological" doses has an effect on the mobilization of the bone salt (CARLSSON 1952, 1954; LINDQUIST; CARLSSON and LINDQUIST); these results have been recently reviewed in the light of certain observations on the mechanism of isotope fixation in bone (BAUER, CARLSSON and LINDQUIST). Against the background of our earlier findings there were good reasons for a new investigation into the mode of action of dihydrotachysterol, especially in relation to vitamin D.

Experimental Conditions

Two diets were employed. The high-Ca diet contained 1.48 per cent Ca and 0.25 per cent P (cf. LINDQUIST), the low-Ca diet 0.04 per cent Ca and 0.48 per cent P (cf. CARLSSON 1952).

Twenty-five-day-old rats of both sexes were transferred to one of these diets. After 21 days on the experimental diet, the rats received a single dose of dihydrotachysterol or vitamin D_2, given in 0.5 ml peanut oil by means of a stomach tube. The control groups received 0.5 ml peanut oil only. The solutions of dihydrotachysterol[1] and vitamin D_2 (the British Drug Houses) were made from crystalline substances. After a suitable interval, usually 4 days, labelled Ca in the form of the lactate—20 mg Ca unless otherwise stated— was given, also by stomach tube, and the animals were killed 18 hours later by bleeding under ether anesthesia. The animals were fasted 4 hours before and 3 hours after the administration of Ca^{45}.

The gastrointestinal tract and various calcified tissues were collected and ashed. The urine and faeces of each rat had been collected separately, and the faeces were added to the specimen of the digestive tract. For measurements of radioactivity the samples

TABLE 1

Skeletal uptake and urinary excretion of Ca^{45} when given orally at varying intervals after administration of dihydrotachysterol (DHT) to rats kept on a high calcium diet.

The values indicate mean ± standard error of the mean. The serum Ca was determined in pooled samples.

Interval DHT–Ca^{45}, days	No. of rats	Body weight g	Ca^{45} % of dose			Serum Ca mg per 100 ml
			Femur	Incisors	Urine	
Control	6	79.2 ±2.5	0.32 ±0.02	0.57 ±0.02	6.7 ±0.4	11.7
1/4	2	70.5 ±4.5	0.63 ±0.05	1.47 ±0.32	15.1 ±0.7	10.4
1/2	2	70.5 ±0.5	0.82 ±0.02	1.59 ±0.16	13.7 ±0.1	11.7
1	2	74.5 ±1.5	0.81 ±0.09	1.61 ±0.17	15.2 ±0.2	9.8
2	2	69.5 ±5.5	1.30 ±0.06	1.15 ±0.05	11.1 ±1.3	—
4	2	76.5 ±4.5	1.43 ±0.04	0.84 ±0.03	11.8 ±1.2	10.9
6	2	79.5 ±10.5	1.50 ±0.03	0.74 ±0.02	7.6 ±1.1	11.9

[1] Kindly supplied by E. Merck, Chemische Fabrik, Darmstadt, Germany.

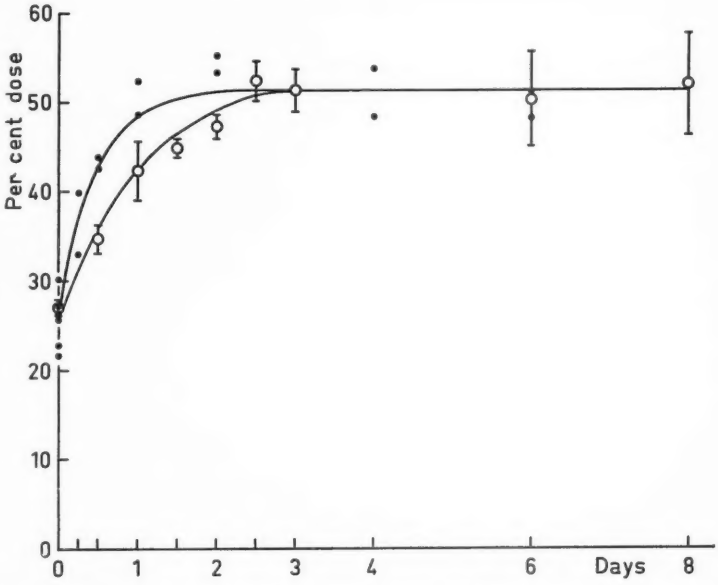

Fig. 1. The absorption of Ca^{45} when given orally at varying intervals after the administration of dihydrotachysterol or vitamin D to rats on a high-calcium diet.—Mean values obtained after the administration of calciferol in a dose of 15 I.U. (= 0.375 μg) are indicated by circles ($\pm$standard error of the mean). The dots are single values obtained after dihydrotachysterol in a dose of 300 μg.

Note.—The somewhat more rapid onset of action of dihydrotachysterol may be referable to the comparatively large dose of this sterol.

were dissolved in dilute nitric acid. The technique followed was that of CARLSSON (1951). The serum Ca was estimated according to CLARK and COLLIP.

Four series of experiments were carried out. In the first series dihydrotachysterol was given to rats on the high-Ca diet at a varying interval ($\frac{1}{4}$–6 days) before the administration of the radiocalcium. The dose of dihydrotachysterol given was 300 μg (Table 1, Fig. 1). In the second series each of the animals received dihydrotachysterol in doses varying from 0.03 to 3,000 μg. This experiment was carried out on rats fed on the high-Ca diet (Table 2, Fig. 2) or on the low-Ca diet (Table 3). The rats on the low-Ca diet received 5 (instead of the usual 20) mg Ca. The third series consisted, besides the control group, of 6 groups on the low-Ca diet, 3 groups receiving 30, 300 and 3,000 μg dihydrotachysterol, respectively, and the remaining 3 groups 10, 100 and 1,000 I.U. (1,000 I.U. = 25 μg) vitamin D, respectively (Fig. 3). The fourth series comprised 2 subseries, one carried out in intact rats on the low-Ca diet (Fig. 4), the other in rats parathyroidectomized 5 days before the administration of the isotope; they were fed on the high-Ca diet (Fig. 5). The doses of dihydrotachysterol and vitamin D given were 30 μg and 100 I.U. (= 2.5 μg), respectively.

TABLE 2

Effect of varying doses of dihydrotachysterol (DHT) on the absorption, skeletal uptake, and urinary excretion of Ca^{45} in rats on a high-calcium diet.

The values indicate mean ± standard error of the mean. The serum Ca was determined in pooled samples.

DHT μg	No. of rats	Body weight g	Ca^{45} % of dose				Serum Ca mg per 100 ml
			Absorption	Femur	Incisors	Urine	
—	2	62.5 ±0.5	25.4 ±1.3	0.23 ±0.04	0.69 ±0.08	6.7 ±0.6	10.7
0.03	2	62.5 ±1.5	27.5 ±3.0	0.27 ±0.03	0.75 ±0.04	9.0 ±0.3	9.8
0.3	2	62.5 ±2.5	31.1 ±2.7	0.35 ±0.03	0.80 ±0.06	9.1 ±0.6	10.0
3	2	62.5 ±3.5	54.1 ±1.3	1.02 ±0.14	1.08 ±0.02	14.7 ±0.6	10.8
30	2	60.0 ±9.0	52.4 ±0.7	1.25 ±0.11	0.94 ±0.08	12.6 ±1.2	14.1
300	2	63.0 ±1.0	54.4 ±2.9	1.33 ±0.15	1.00 ±0.05	10.8 ±1.2	13.0

TABLE 3

Effect of varying doses of dihydrotachysterol (DHT) on the absorption, skeletal uptake, and urinary excretion of Ca^{45} in rats on a low-calcium diet.

The values indicate mean ± standard error of the mean. The serum Ca was determined in pooled samples.

DHT μg	No. of rats	Body weight g	Ca^{45} % of dose				Serum Ca mg per 100 ml
			Absorption	Femur	Incisors	Urine	
—	4	73.5 ±3.5	31.0 ±2.3	1.38 ±0.08	1.00 ±0.09	0.20 ±0.03	4.6
0.03	4	72.8 ±2.9	28.4 ±1.7	1.35 ±0.11	0.97 ±0.05	0.17 ±0.03	5.2
0.3	3	75.0 ±5.1	48.1 ±2.3	1.71 ±0.04	1.20 ±0.03	0.23 ±0.08	7.0
30	3	79.7 ±4.9	83.9 ±0.9	4.24 ±0.25	2.44 ±0.11	0.27 ±0.04	8.6
3,000	4 [1]	—	—	—	—	—	—

[1] All the animals died.

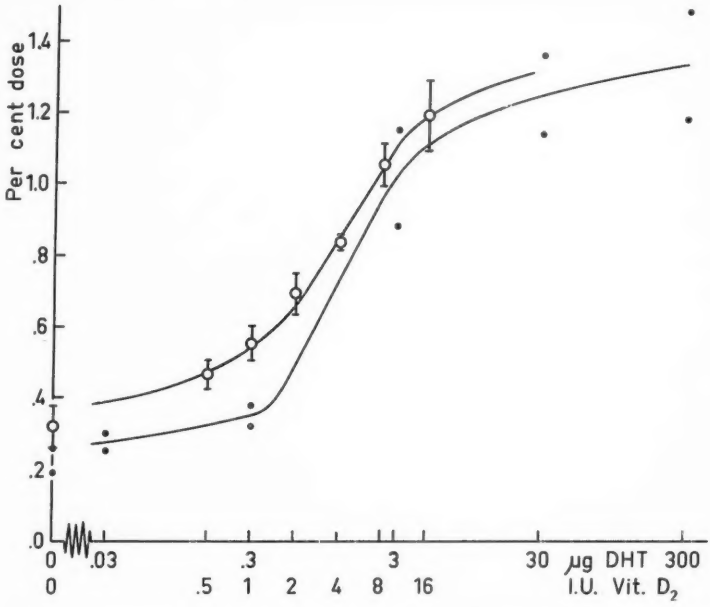

Fig. 2. Effect of varying doses of dihydrotachysterol (DHT) and vitamin D on the uptake of Ca^{45} in the femur of rats on a high-calcium diet.—The symbols are the same as in Fig. 1.

Results

The administration of dihydrotachysterol was followed by a gradual increase in the absorption of Ca^{45} (Table 1) and in the femur Ca^{45} (Fig. 1), the effect being fully developed within a few days. In this respect dihydrotachysterol resembles vitamin D (the data on vitamin D shown in Fig. 1, as well as those shown in Fig. 3, are taken from LINDQUIST).

LINDQUIST observed that about 10 I.U. of vitamin D were enough for a full effect on the absorption of Ca, larger doses having but a slight additional effect. The corresponding dose of dihydrotachysterol appears to be of the order of 3 to 30 μg (Tables 2 and 3, Fig. 3). The femur Ca^{45} behaved in a similar manner. The shape of the dose-response curve, as studied within the therapeutical dosage range, resembled that of vitamin D (Fig. 2). In the second series all the animals receiving 3,000 μg of dihydrotachysterol died (Table 3), while in the third series (Fig. 3) 4 out of the 6 animals receiving this dose of dihydrotachysterol died, the remaining 2 animals being in a bad condition.

The influence of vitamin D on the serum Ca continued to increase with the dose even after the effect on the absorption of Ca had reached a plateau (Fig.

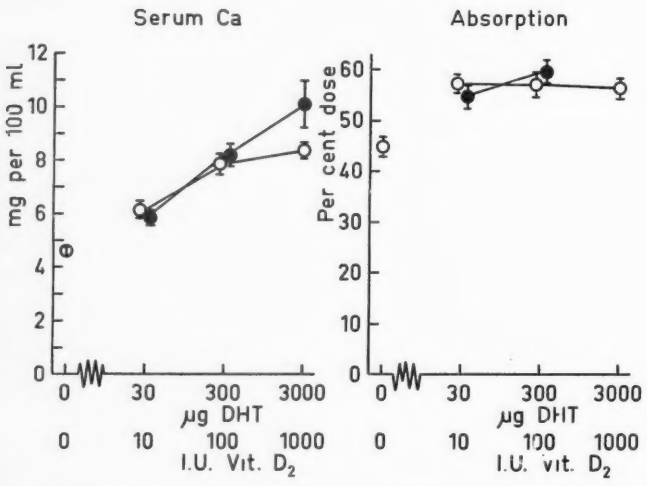

Fig. 3. Effect of varying doses of dihydrotachysterol (DHT) (solid symbols) and vitamin D (open symbols) on the serum calcium level and on the absorption of Ca^{45} in rats on a low-calcium diet.— The symbols indicate mean ± standard error of the mean.

Dihydrotachysterol	No. rats	Vitamin D_2	No. rats
30 µg	10	10 I.U.	9
300 µg	4	100 I.U.	4
3,000 µg	2	1,000 I.U.	6

(10 controls)

Six rats were given 3,000 µg dihydrotachysterol. Four of these animals died and the remaining 2 rats were sick and received no Ca^{45}.

3; cf. CARLSSON and LINDQUIST). Dihydrotachysterol behaved in a similar manner. Thirty µg of dihydrotachysterol were found to have the same action on the serum Ca level as 10 to 100 I.U. (=0.25 to 2.5 µg) of vitamin D (Figs. 2, 4, and 5). Thus the ratio between the smallest effective doses of the two sterols appeared to be the same, whether the action on the serum Ca or the effect on the intestinal absorption of Ca was considered.

The two sterols had the same influence on the skeletal distribution of Ca^{45}, the ends of the long bones being affected more than the shafts (Figs. 4 and 5). It was also noted that dihydrotachysterol, like vitamin D, increased the femur Ca^{45} more than the incisors Ca^{45} (Tables 1 to 3).

The results did not differ essentially, whether diets rich or poor in Ca were used, or whether the parathyroids were intact or absent (Figs. 4 and 5).

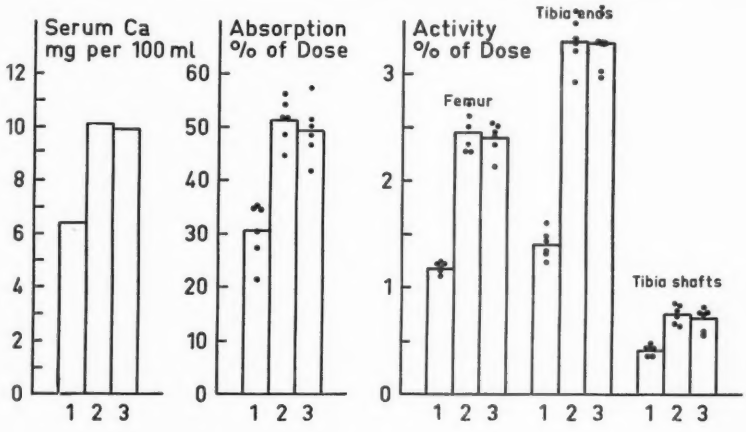

Fig. 4. Effect of dihydrotachysterol and vitamin D on the serum Ca level and on the absorption and skeletal distribution of Ca^{45} in rats on a low-Ca diet.—1, untreated animals; 2, dihydrotachysterol 30 μg; 3, vitamin D_2 100 I.U. The dots indicate single observations. The serum Ca was determined on pooled samples.

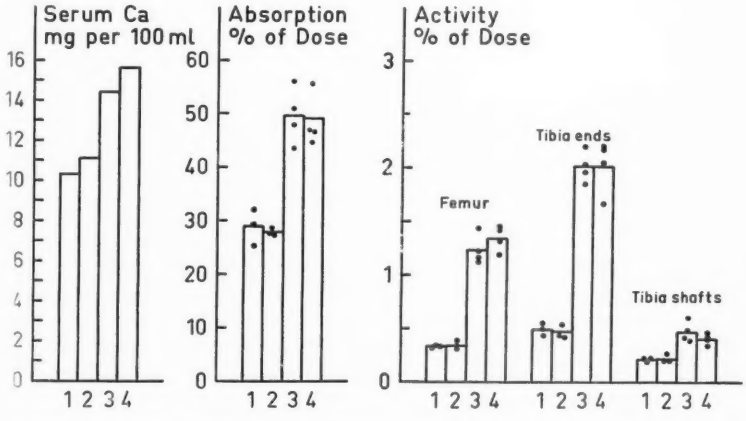

Fig. 5. Effect of dihydrotachysterol and vitamin D on the serum Ca level and the absorbtion and skeletal distribution of Ca^{45} in intact and parathyroidectomized (pthect.) rats on a high-Ca diet.—1, untreated animals; 2, pthect.; 3, pthect. + dihydrotachysterol 30 μg; 4, pthect. + vitamin D_2 100 I.U. The dots indicate single observations. The serum Ca was determined on pooled samples.

Discussion

As demonstrated by SHOHL and coworkers (l.c.) ,dihydrotachysterol differs markedly from vitamin D in two respects: (1) the dose required to cure rickets is higher, and (2) the therapeutic range is narrower. The present experiments are in agreement with these observations.

In suitable dosage the antirachitic action of dihydrotachysterol should be as satisfactory as that of vitamin D. In fact, human rickets, of the type relatively refractory to vitamin D, has been successfully treated with dihydrotachysterol (VAN CREVELD and ARONS).

It has been claimed that dihydrotachysterol differed from vitamin D in having a stronger bone-salt mobilizing action relative to the effect on the intestinal absorption, or, to use the vocabulary of ALBRIGHT, more phosphorus-excretion-effect per unit calcium-absorption-effect. In the light of the present experiments this description does not seem adequate. In small doses, falling within the therapeutic range, the two sterols did not differ with respect to relative effects on the intestinal absorption and on the bone resorption (as indicated by the serum Ca). On the other hand, with increasing doses the effect of both sterols on the bone resorption (relative to the intestinal action) became more dominant. This influence of dosage is more marked for dihydrotachysterol than for vitamin D, only in so far as the dose-response curve is steeper for the former compound.

It is thus questionable whether the actions of dihydrotachysterol and vitamin D differ in other respects than the two mentioned above. So far no explanation can be offered for the narrower therapeutic range of dihydrotachysterol. However, it is tempting to suggest that the action of the more "physiological" of the two sterols can be controlled to a certain extent by the organism. Actually, there is some evidence supporting such an assumption: the effect of a "physiological" dose of vitamin D on the absorption of Ca was absent in rats with amply filled bone stores (CARLSSON 1953), indicating that the organism is capable of controlling the action of the vitamin according to its needs. It does not seem unreasonable to assume that this control mechanism is responsible for the unusually wide safety margin of vitamin D; whenever the action of vitamin D tends to exceed the optimum point it may be counteracted by means of this mechanism. According to this line of thought the narrower safety margin of dihydrotachysterol would indicate a very high specificity of the control mechanism as regards the structure of the sterol molecule acted upon. One observation consistent with this hypothesis but otherwise perhaps difficult to explain, is the almost identical shape of the dose-response curves of the two sterols *within the therapeutic dose range*; the different shape of the two curves is thus apparent only in the toxic dose

range. In animals with empty bone stores, such as those of the present investigation, the activation of the hypothetical control mechanism, resulting in an inhibition of the action of vitamin D, would be likely to occur only in high dosage.

Summary

In experiments on rats it was found that dihydrotachysterol differs markedly from vitamin D in two respects: (1) the dose required to cure rickets is higher, and (2) the therapeutic range is narrower.

In respect to the effect of proper dosage, the authors were not able to confirm earlier claims that dihydrotachysterol differs from vitamin D_2 in having a stronger bone-salt mobilizing effect relative to the action on Ca absorption.

There seems to be no reason to believe that dihydrotachysterol should be preferable to vitamin D in hypoparathyroidism or other hypocalcemic conditions.

This investigation was aided by grants from the Swedish State Medical Research Council.

Une étude comparative sur le mode d'action du dihydrotachystérol sur le metabolisme du calcium.

On a découvert par des expériences sur des rats que le dihydrotachystérol diffère nettement de la vitamine D sous deux aspects : 1) la dose nécessaire à la guérison du rachitisme est plus élevée, et 2) la marge thérapeutique est plus étroite. Les auteurs n'ont pas pu, en observant soigneusement l'effet du dosage, confirmer l'opinion avancée précédemment que le dihydrotachystérol présenterait une différence avec la vitamine D_2 : il aurait, en ce qui concerne l'action sur l'absorption du calcium, une influence plus accentuée sur la mobilisation des sels dans les os. Il semble qu'il n'y ait pas de raison de croire que le dihydrotachystérol soit préférable à la vitamine D dans l'hypoparathyroidie ou d'autres états hypocalcémiques.

Vergleichende Untersuchungen über die Wirkung von Dihydrotachysterol und Vitamin D auf den Calcium-Haushalt.

Durch Untersuchungen an Ratten wurde gefunden, dass Dihydrotachysterol sich in zweierlei Hinsicht deutlich vom Vitamin D unterscheidet, 1) die erforderliche Dosis zur Heilung von Rachitis ist höher, 2) die therapeutische Breite ist enger. Indem die Autoren den therapeutischen Erfolg der Dosierung genau betrachteten, waren sie nicht in der Lage, früheren Aussagen zuzustimmen, dass Dihydrotachysterol sich vom Vitamin D_2 dadurch unterschiede, dass es einen stärkeren knochensalzmobilisierenden Effekt bezüglich der Wirkung auf die Calciumabsorption habe. Es scheint kein Grund zu bestehen, dass Dihydrotachysterol bei Hypoparathyreoidismus oder anderen hypocalkämischen Zuständen Vitamin D vorgezogen werden sollte.

Estudio comparativo del modo de acción del dihidrotaquisterol y la vitamina D sobre el metabolismo del calcio.

En experiencias con ratas se encontró que el dihidrotaquisterol difiere marcadamente de la vitamina D en dos aspectos: 1) la dosis requerida para curar el raquitismo es mayor, 2) el margen terapéutico es menor. Considerando el efecto de un dosaje

adecuado, los autores no pudieron confirmar que el dihidrotaquisterol se diferencia de la vit. D_2 en tener una acción movilizadora sobre las sales óseas en relación con la absorción de calcio. Parecería no haber razón para creer que el dihidrotaquisterol debe preferirse a la vit. D en hipoparatiroidismo u otras condiciones con hipocalcemia.

References

Albright, F., Bloomberg, E., Drake, T. and Sulkowitch, H. W.: A comparison of the effects of A.T. 10 (dihydrotachysterol) and vitamin D on calcium and phosphorus metabolism in hypoparathyroidism. J. Clin. Invest. *17:* 317, 1938.

Albright, F., Sulkowitch, H. W. and Bloomberg, E.: A comparison of the effects of vitamin D, dihydrotachysterol (A.T. 10) and parathyroid extract on the disordered metabolism of rickets. Ibid. *18:* 165, 1939.

Albright, F. and Reifenstein, E. C.: Parathyroid Glands and Metabolic Bone Disease. The Williams and Wilkins Company, Baltimore 1948.

Bauer, G. C. H., Carlsson, A. and Lindquist, B.: Evaluation of accretion, resorption, and exchange reactions in the skeleton. Kgl. Fysiograf. Sällskap. Lund Förh. *25*, nr. 1, 1955.

Carlsson, A.: Metabolism of radiocalcium in relation to calcium intake in young rats. Acta pharmacol. et toxicol. *7:* Suppl. 1, 1951.

—— Tracer experiments on the effect of vitamin D on the skeletal metabolism of calcium and phosphorus. Acta physiol. Scand. *26:* 212, 1952.

—— Experiments with radiocalcium on the interrelationships between vitamin D and dietary calcium and phosphorus. Acta pharmacol. et toxicol. *9:* 32, 1953.

—— The cause of hypophosphatemia and hypocalcemia in vitamin D deficiency. Acta physiol. Scand. *31:* 308, 1954.

Carlsson, A. and Lindquist, B.: Comparison of intestinal and skeletal effects of vitamin D in relation to dosage. Ibid. 1955 (in press).

Clark, E. P. and Collip, J. B.: A study of the Tisdall method for the determination of blood serum calcium with a suggested modification. J. Biol. Chem. *63:* 461, 1925.

Correll, J. T. and Wise, E. C.: Antirachitic properties of A.T. 10 for the rat and chicken. J. Nutrition *23:* 217, 1942.

van Creveld, S. and Arons, Ph.: Transitory renal osteoporosis with amino-aciduria and development of a hypersensitivity to vitamin D. Annales paediatrici *173:* 299, 1949.

Latta, J. S. and Tristan, T. A.: Alterations in long bones of young albino rats induced by dihydrotachysterol (Hytakerol). Proc. Soc. Exp. Biol. Med. *75:* 403, 1950.

Lindquist, B.: Effect of vitamin D on the metabolism of radiocalcium in rachitic rats. Acta paediat. *41:* Suppl. 86, 1952.

McLean, F. C.: Activated sterols in the treatment of parathyroid insufficiency. J.A.M.A. *117:* 609, 1941.

Shohl, A. T., Fan, C. H. and Farber, S.: Effect of A.T. 10 (dihydrotachysterol) on various types of experimental rickets in rats. Proc. Soc. Exp. Biol. Med. *42:* 529, 1939.

Shohl, A. T. and Farber, S.: Effect of A.T. 10 (dihydrotachysterol) on rickets in rats produced by high-calcium–low-phosphorus diets. J. Nutrition *21:* 147, 1941.

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Idiopathic Hypercalcaemia of Infancy

Studies of the Mineral Balance

by WILLIAM B. MACDONALD and THOMAS STAPLETON

Idiopathic hypercalcaemia in infancy was described by LIGHTWOOD (1952) to the British Paediatric Association, and on the same occasion PAYNE outlined the chemical changes. FANCONI, GIRARDET, SCHLESINGER, BUTLER and BLACK described two cases of the disturbance with certain complicating features including mental retardation and osteosclerosis, and SCHLESINGER, BUTLER and BLACK added five more such cases. CREERY, CREERY and NEILL, DAWSON and CRAIG, FERGUSON and MCGOWAN, HARRIS (1954), LOWE, HENDERSON, PARK and MCGREAL, RUSSELL, YOUNG, JACOBY and DOBBS, and STAPLETON and EVANS have also described cases of idiopathic hypercalcaemia in infancy, some simple and others with the complicating features.

The purpose of this paper is to present observations made on three infants with idiopathic hypercalcaemia. The changes in serum chemistry were followed in all three cases, and balance studies were made on the two male infants, before, during and after various treatments.

Case Histories

Case I. A. Gd. was a male infant first admitted to St. Mary's Hospital on 27th April 1954, at the age of 9 months, because of failure to thrive since the age of 3 months.

He was the first-born child of an apparently healthy mother, who had taken calcium tablets, but no vitamin D supplements, during the pregnancy. He was born two weeks before the expected date of delivery, birth weight 2330 g. He was breast-fed for 5 weeks and was then given Ostermilk No. 1, a modified dried milk containing not less than 320 i.u. Vitamin D per dry ounce, until the age of 3 months, when he was changed to Full-Cream National Dried Milk, containing not less than 280 i.u. Vitamin D per dry ounce, and was given one teaspoonful of cod liver oil compound (700 i.u. Vitamin D per teaspoonful) and half a teaspoonful of orange juice daily. He progressed well until the age of 3 months, when he weighed 5450 g. From 3–6 months he vomited and was constipated. At the age of $6^1/_2$ months he was admitted to another hospital

for investigation of a suspected urinary infection. His weight was still 5450 g. Urine microscopy showed 5–10 pus cells/HPF, but culture was sterile, and retrograde pyelography was normal. His blood urea was 99 mg/100 ml. Serum electrolyte concentrations were reported as normal, but the serum calcium was not estimated. Mixed feeding was started at 7 months. Vitamin D supplements were stopped at $8^1/_2$ months.

He was seen at St. Mary's Hospital aged 9 months. He weighed 5910 g, was not dehydrated, was alert and active, but was hypotonic and unable to sit up without support. The deep reflexes were active. There was no cardiac murmur or hypertension. Radiological examination of the long bones showed fine transverse lines at the metaphyses. He had a mild normocytic anaemia. The urine contained a trace of albumin and a few pus cells. There was no glycosuria or aminoaciduria. The blood urea was 102 mg/100 ml. The serum calcium was 15.6 mg/100 ml.

Balance studies were done on a Full-Cream National Dried Milk, and then on a cow's milk diet, no Vitamin D supplements being given. As he made only slight clinical improvement, his serum calcium remained high, and his blood urea rose further, he was put on a calcium-free milk, prepared by passing cow's milk through a cation exchange resin column, as described by DENT (10). This milk was also magnesium-free. He showed both clinical and biochemical improvement and was discharged from hospital aged 11 months, weighing 7050 g, on Full-Cream Cow and Gate Dried Milk, which had not been fortified with Vitamin D.

He soon became unwell again and was readmitted to hospital, vomiting, constipated and having lost weight. On this occasion he was given oral cortisone (200 mg daily for 28 days). Clinical and biochemical improvement occurred. This was maintained whilst on a synthetic calcium-free milk (Trufood) and calcium-free cereal (Glaxo) with no added Vitamin D. The low calcium diet was administered for four months, when a full diet, with no Vitamin D supplements, was substituted without ill effect.

During his stay in hospital, ten balance studies each lasting four days were done. Improvement in the later stages of the illness may have been due to natural recovery, but the rapid responses to the institution and withdrawal of treatment earlier in the course of the illness appeared to be due to the treatments themselves.

Case II. J. Cl., a male infant, was admitted to St. Mary's Hospital on 2nd August 1954, aged 16 months, because of intermittent vomiting for 12 months, and failure to thrive for 9 months.

A full-term infant, the third child in a healthy family, he weighed 2920 g at birth. His mother had not taken calcium or vitamin supplements during pregnancy. He was breast fed for one month. After ten days on half strength cow's milk, his feeding was changed to Half-Cream Cow and Gate dried milk, and at the age of $3^1/_2$ months to Full-Cream Cow and Gate dried milk, each containing not less than 320 i.u. Vitamin D per dried ounce. At 4 months of age vomiting started. He was still fed on either Half- or Full-Cream Cow and Gate dried milk. Supplements had been offered only after commencement of his illness, and rose hip syrup alone had been accepted. Solid foods had been offered at the age of 8 months, but he was reluctant to take them.

At the age of 14 months he was admitted to a hospital because of the continued vomiting and failure to thrive. A diagnosis of idiopathic hypercalcaemia of infancy was made (serum calcium 14.0, 14.0, 13.7, 12.0 mg/100 ml).

When examined at St. Mary's Hospital he weighed 8750 g, was normally hydrated and seemed content and alert. He was hypotonic, and would not remain sitting or standing. His deep reflexes were active. The systolic blood pressure was 140 mm. Hg. His heart was normal in size, but there was a loud harsh murmur, occupying most of

systole, and audible over the whole precordium. There was also a short apical diastolic murmur. Radiography and electrocardiography did not show any evidence of congenital heart disease. His skeletal and skull measurements were normal for his age, but the skull sutures were prominent and the fontanelles closed. Radiological examination showed a band of condensation at the metaphysis of each long bone. Urine was normal on microscopy and culture. There was no proteinuria, glycosuria or amino aciduria. The serum calcium level was only slightly raised to 11.9 mg/100 ml and the blood urea was 61 mg/100 ml. As his serum calcium had been raised on four successive occasions and the clinical features were characteristic, there was no reason to doubt that he was suffering from idiopathic hypercalcaemia.

He was given a diet of whole cow's milk, without added Vitamin D, and while on this, oral cortisone 200 mg daily for 14 days. Subsequently he was given a calcium-free milk (Trufood) and calcium-free cereal (Glaxo), with no added Vitamin D, for 2 months. During this period of three months he improved clinically, although the cardiac murmur persisted. His weight increased steadily after an initial rise on cortisone. On return to a full diet, improvement was maintained, and at the age of 21 months he was behaving like a normal child and walking. From the time of his admission to St. Mary's Hospital, his serum biochemistry was only slightly abnormal, and at the time of discharge was quite normal. Whilst in hospital, six balance studies, each lasting four days, were made. It seems probable that the start of observations coincided with the commencement of natural remission and it is likely that treatment aided, rather than initiated, improvement.

Case III, P. Ct., a girl, was admitted to St. Mary's Hospital on 18 th May 1954, at the age of 25 months, because of failure to thrive normally since the age of 10 weeks.

She was a first-born full-term infant, birth weight 3070 g, who had been shocked at birth, requiring oxygen for resuscitation. Her mother had taken calcium and vitamin supplements during her pregnancy. The breast feeding had to be complemented from birth and by 9 weeks of age she was fed entirely on Ostermilk No. 1, containing not less than 320 i.u. Vitamin D per dried ounce. Because of vomiting, the feed was changed to Full-Cream Cow and Gate dried milk, containing not less than 320 i.u. Vitamin D per dried ounce, then to Half-Cream National Dried Milk, and later to Full-Cream National Dried Milk, both containing not less than 280 i.u. Vitamin D per dried ounce, but the symptoms persisted. She was given cod liver oil compound (700 i.u. Vitamin D per teaspoonful) daily from birth taking 1 teaspoonful per day from the age of 3 to 6 months. Adexolin 10 drops (625 i.u. Vitamin D) per day was then substituted for 2 months, when supplements were discontinued.

At the age of 8 months, she was admitted to hospital because of persistent vomiting. She was underweight, dehydrated and constipated. Her development was retarded and she was unable to sit unsupported. She had hypertension, a systolic murmur, pyuria, a blood urea of 41 mg/100 ml, and a serum calcium of 14.4 mg/100 ml. The symptoms persisted: she remained underweight, her skeletal and skull growth was retarded, and radiographs showed osteosclerosis of skull and long bones. The peculiar facies associated with severe grades of chronic hypercalcaemia with osteosclerosis developed. Mental retardation was obvious. The high serum calcium, blood urea and serum cholesterol persisted.

She was transferred to St. Mary's Hospital at the age of 2 years 1 month where the clinical and biochemical abnormalities were confirmed. She weighed 6360 g. The serum calcium was 13.9 mg/100 ml and blood urea was 181 mg/100 ml. Treatment with cortisone and a calcium-free milk (Trufood), with no added Vitamin D, resulted in a

fall of serum calcium and a lowering of the blood urea. There was considerable diminution in osteosclerosis of the long bones.

At the age of 3 years, despite these improvements, she remains undersized, underweight, hypotonic and mentally retarded. Anorexia is extreme and vomiting can be avoided only by tube feeding. The systolic blood pressure is 120 mm Hg, a systolic cardiac murmur is still audible, but there is no radiological evidence of cardiac calcification. Craniostenosis with early papilloedema is developing. Her urine is free from pus or bacilli, but contains casts. She does not become dehydrated if vomiting is avoided, but is still constipated. She weighs 8070 g, is 76.8 cm in length, and her skull circumference is 46 cm. She can say a few words, but she is unable to construct sentences. She cannot stand even with support.

Her serum calcium is normal (10.7 mg/100 ml), and blood urea 80 mg/100 ml.

Methods of Analyses

Serum calcium—STANFORD and WHEATLEY modification of KRAMER and TISDALL, using 2.0 ml of serum. Serum inorganic phosphate—KING using 0.2 ml serum. Serum magnesium—ORANGE and RHEIN using 0.1 ml serum. Blood urea—ARCHER and ROBB using 0.2 ml blood. Serum cholesterol—SACKETT using 2.0 ml serum. Serum proteins—Biuret method (HARRISON "Chemical Methods in Clinical Medicine") using 0.2 ml serum. Serum alkaline phosphatase—KING and ARMSTRONG using 0.5 ml serum.

Urine calcium—TISDALL and KRAMER. Urine total phosphorus—FISKE and SUBBA ROW. In both procedures, the urine was digested with concentrated sulphuric acid and hydrogen peroxide. Urine magnesium—modification of GARNER.

Faeces were preserved for the four-day balance period, homogenized, allowed to stand with concentrated sulphuric acid, and made up to a volume of 500 or 1000 mls. Two ml aliquots were digested and estimated as for urine. Two ml aliquots of milk were digested and estimated as for urine. Accurately weighed aliquots of cereal, approximately 0.2 g, were digested and estimated as for urine. Mixed diets were homogenized and weighed accurately. Aliquots were weighed wet and dry and approximately 0.5 g of dried homogenate was weighed accurately, digested and estimated as for urine.

Recovery analyses confirmed the absence of calcium in the calcium-free milk and cereal.

Phytic acid—MCCANCE and WIDDOWSON.

Pre-Treatment Observations

The serum calcium and blood urea were raised, especially in the two more severely affected infants (Cases I and III).

The serum inorganic phosphorus was slightly raised in the more severely affected male infant (Case I), but normal in the other two.

The serum magnesium was at the upper limit of normal in Cases I and III, but normal in Case II.

When fed on Full-Cream National Dried Milk, or on whole cow's milk, with no added Vitamin D, Case I was in strongly positive calcium and

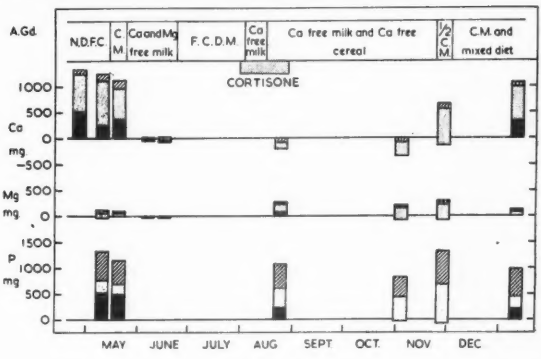


Fig. 1.

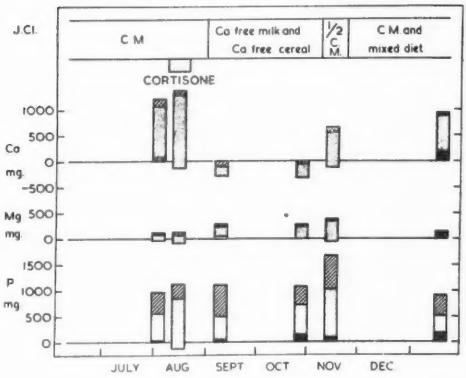


Fig. 2.

Figs. 1 and 2. *Cases I, II.* Treatment related to calcium, magnesium and phosphorus balances. The daily balance which is the average of a four-day collection is shown.

Hatched areas represent urinary excretion.
Dotted areas represent faecal excretion.
Black areas represent positive balance.

Symbols used in Figs. 1–8:

N.D.F.C. = Full-Cream National Dried Milk, containing not less than 280 i.u. Vitamin D per dried ounce.
C.M. = Homogenised cow's milk, with no added Vitamin D.
Ca and Mg free milk = Calcium and magnesium free column-prepared milk, with no added Vitamin D.
F.C.D.M. = Cow and Gate Full-Cream Dried Milk, with no added Vitamin D.
Ca free milk = Glaxo or Trufood synthetic calcium-free milk, with no added Vitamin D.
Ca free cereal = Glaxo synthetic calcium-free cereal, with no added Vitamin D.
Cortisone = 200 mg cortisone orally per day.

phosphorus balance whilst the magnesium balance approached equilibrium (Fig. 1). When fed on whole cow's milk with no added Vitamin D, Case II was in slightly positive calcium balance; the phosphorus and magnesium

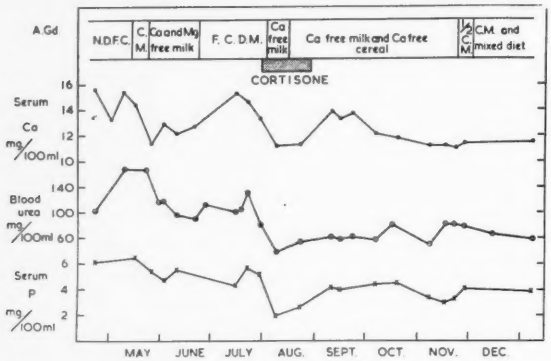
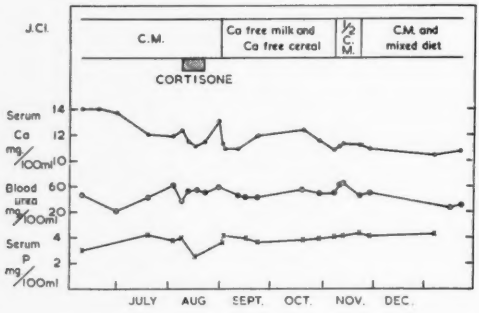


Fig. 3.



Figs. 3–5. *Cases I, II, III.* Treatment related to serum calcium, blood urea and serum phosphorus. *For symbols see Figs. 1–2.*

Fig. 4.

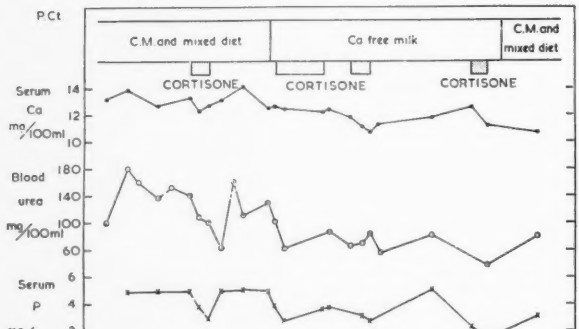


Fig. 5.

balances were in equilibrium (Fig. 2). In both infants urine calcium excretions were high (Figs. 6 and 7). Renal function tests were not done, and assessment of function was made on blood urea levels alone.

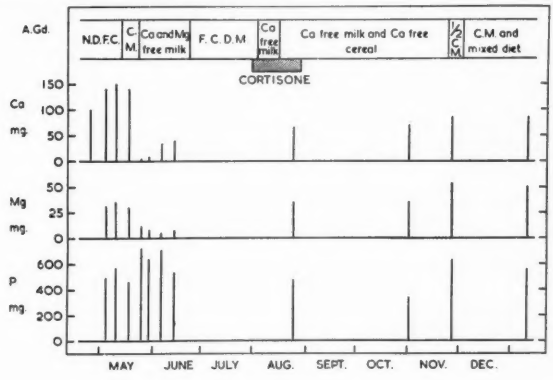


Fig. 6.

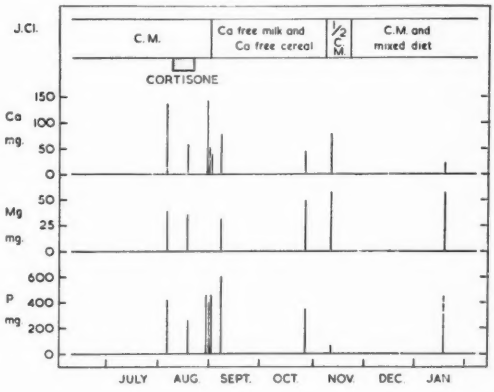


Fig. 7.

Figs. 6 and 7. *Cases I, II.* Treatment related to 24-hour urine calcium, magnesium and phosphorus excretions. (Where the collections were in four-day periods, the average daily excretion is shown.) *For symbols see Figs. 1–2.*

Observations during Treatment

1. *Column Prepared Calcium-Free Milk*

One infant (Case 1) was fed on whole cow's milk which had been passed through a column containing a cation exchange resin (Zeocarb 215) in the sodium, potassium cycle. The milk thus became calcium- and magnesium-free, and observations were made during the change over from whole cow's milk to this milk.

There were rapid falls in serum calcium, magnesium and inorganic phosphorus, and blood urea (Figs. 3, 8). The serum calcium and phosphorus rose slightly within a week, but to much lower levels than before treatment. Serum magnesium and blood urea remained down although the latter was still above normal. After administration of calcium-free column prepared milk for one month, feeding was changed to a Vitamin D-free Cow and

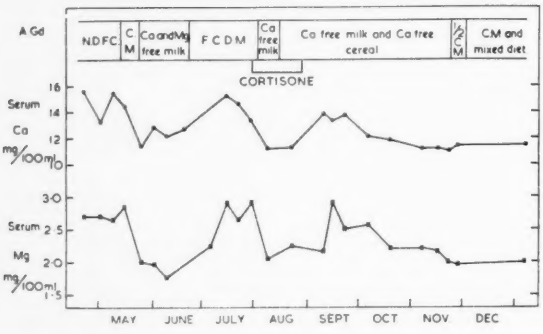


Fig. 8. *Case I.* Treatment related to serum calcium and serum magnesium. *For symbols see Figs. 1–2.*

Gate Full-Cream Dried Milk. Within a short time, the serum calcium and magnesium had returned to pre-treatment levels, and there was a rapid rise in blood urea, but not to the previous level. Serum phosphorus was not altered significantly.

During the transition from whole cow's milk to column prepared calcium-free milk, observations were made on the excretion of calcium, magnesium and phosphorus in serial twenty-four hour specimens of urine (Fig. 6). There was a contrast in the behaviour of all three electrolytes. Urine calcium excretion fell to very low levels immediately, coincident with the rapid fall in serum calcium. Despite continuation of a calcium-free diet for four weeks, excretion gradually increased, but only to one quarter of the pre-treatment level.

Magnesium excretion gradually decreased until conservation was almost complete. Excretion of magnesium was still falling whilst that of calcium was rising.

At the time of the shut down of calcium excretion, urine phosphorus excretion increased immediately by approximately 150–200 mg per 24 hours, although there was no increase in intake.

Two balance studies during the period on column prepared calcium-free milk showed a small negative balance of calcium and an insignificant negative magnesium balance (Fig. 1). No phosphorus balance was done during these two periods.

2. *Synthetic Calcium-Free Milk and Calcium-Free Cereal*

The three infants received synthetic calcium-free diets with no added Vitamin D for several months. The severely ill female (Case III) was fed on milk alone as she refused to take cereal.

Balance studies on Cases I and II demonstrated considerable negative balances of calcium on the combined calcium-free milk and cereal diets.

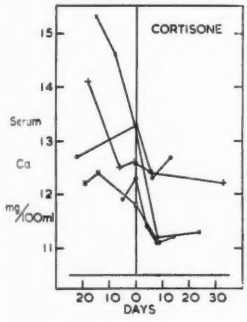


Fig. 9.

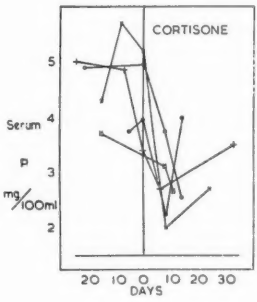


Fig. 10.

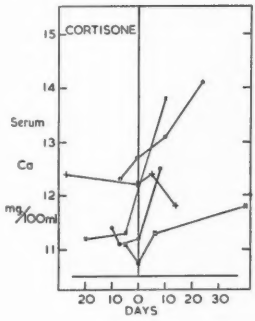


Fig. 11.

Figs. 9–12. Changes in serum calcium and phosphorus when cortisone was started (9–10) and when cortisone was stopped (11, 12). *Case I*, ×; *Case II*, +; *Case III*, ● ○ ☼.

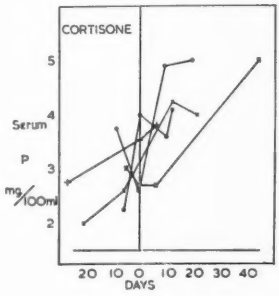


Fig. 12.

In both infants significant negative balances persisted when whole milk was added to these diets (Figs. 1 and 2).

The main loss of calcium was in the faeces and the total loss was much greater than in the balances done on column prepared calcium-free milk (Case I, Fig. 1). It appeared that some constituents of the calcium-free diets were responsible for an increased calcium loss from intestinal secretions. Analysis revealed a high total phosphorus (770, 800 and 670 mg per 100 g dry weight) and a high content of phytic acid (74, 111 and 96 mg phytic acid phosphorus per 100 g) in three synthetic cereals of different composition.

Phosphorus and magnesium balances were either positive or slightly negative in both infants, in contrast to the strongly negative calcium balances.

Urine collections during the transition from whole milk to synthetic calcium-free milk and cereal showed a diminution in excretion of calcium and an increased excretion of phosphorus (Case II, Fig. 7), but not to the same extent as when the diet was changed to column prepared calcium-free milk (Case I, Fig. 6). Observations were not made during the change-over to calcium-free milk and cereal in Case I.

3. *Oral Cortisone*

The three infants received courses of oral cortisone, 200 mg daily for 2–4 weeks. In each instance there was some temporary weight increase due to fluid retention.

In all cases there were falls in serum calcium and phosphorus and blood urea on administration of cortisone, and on withdrawal a return to high levels (Figs. 3–5, 9–12). Withdrawal of cortisone when the infants were on calcium containing diets resulted in return of serum calcium concentrations to higher levels than when the infants were having calcium-free diets. Cortisone had a more rapid and extensive effect, but also a more transient effect on serum concentrations than did a low calcium diet.

Balance studies were made on Cases I and II when receiving cortisone (Figs. 1, 2). Case I at the time was receiving a calcium-free diet and the negative balance obtained could be attributed to this. Phosphorus and magnesium balances were positive.

Cortisone was administered to Case II, when being fed whole cow's milk. Slight negative balances for calcium, magnesium and phosphorus were obtained. Urine excretions of calcium and phosphorus were relatively low whilst cortisone was administered (Fig. 7). Calcium-free diets appeared to be more effective in promoting calcium loss from the body, yet cortisone produced more sudden and steeper falls in serum calcium, phosphorus and blood urea. Falls in serum phosphorus with cortisone were from normal to subnormal levels, not from supernormal to normal levels (Fig. 10).

Observations during Recovery

Balance studies were made on Cases I and II during the recovery phase at the time of clinical improvement and weight gain, when serum calcium, magnesium, phosphorus and blood urea were normal or near normal (Figs. 1, 2). The infants were given full weaning diets, but without vitamin D supplements. Both infants were in positive calcium and phosphorus balance and slightly positive magnesium balance, but urine calcium excretions were much lower than in the pre-treatment phase, notably in Case II, whose recovery was complete (Figs. 6, 7).

Relationships

Throughout the various phases of treatment, a general relationship between serum calcium, phosphorus and blood urea was discernible (Figs. 3, 4, 5). This correspondence was best shown in Case I. Measures which were taken to lower serum calcium also lowered serum phosphorus and blood urea, in parallel.

TABLE 1

Case 1 (A. Gd.).

Date	Age in months	Serum Ca mg%	Serum P mg%	Serum Mg mg%	Blood urea mg%	Proteins g%	Albumin g%	Globulin g%	Cholesterol mg%	Alkaline phosphatase KA units
10. 2.54	6				60					
9. 3.54	7				99					
23. 4.54	9	15.6	6.1	2.7	102					
3. 5.54		13.2		2.7						
10. 5.54		15.4		2.7	168					
17. 5.54		14.4	6.4	2.9	168					
27. 5.54	10	11.4	5.4	2.0	167					
3. 6.54		12.9	4.7	2.0	117	6.5			270	
9. 6.54					100					
11. 6.54		12.1	5.5	1.8						
14. 6.54					96					
21. 6.54	11	12.7			90	6.5				
6. 7.54				2.3						
16. 7.54		15.3	4.3	2.9	100					
19. 7.54					104	5.8	4.0	1.8		
23. 7.54	12	14.6	5.7	2.7	130					
30. 7.54		13.3	5.2	2.9	80					
9. 8.54		11.2	2.0	2.1	38					
23. 8.54	13	11.3	2.6	2.3	57					
11. 9.54		13.8	4.2	2.2	61					
16. 9.54		13.3	4.0	2.9	57					
24. 9.54	14	13.7		2.5	61					
7.10.54		12.1	4.4	2.6	57					
20.10.54	15	11.8	4.6	2.2	80					
8.11.54		11.2	3.4	2.2	50	5.2	4.4	0.8		63
17.11.54		11.2	3.0	2.2	82					60
23.11.54	16	11.0	3.4	2.0	82					36
29.11.54		11.4	4.1	2.0	78					25
15.12.54			4.0		67				184	21
7. 1.55	17	11.5	3.9	2.0	59	7.5	5.0	2.5	250	20
22. 3.55	20	11.6	4.3	2.2	50	6.4	5.0	1.4		17

The 24-hour urine excretions of calcium followed the rise and fall of serum calcium levels.

In Case I, fluctuations in serum magnesium paralleled those of calcium (Fig. 8).

Insufficient serum protein estimations were done during the phases of treatment to draw definite conclusions, but it appeared that there was no

TABLE 2

Case 2 (J. Cl.)

Date	Age in months	Serum Ca mg%	Serum P mg%	Serum Mg mg%	Blood urea mg%	Proteins g%	Albumin g%	Globulin g%	Cholesterol mg%	Alkaline phosphatase KA units
11. 6.54	15	14.0	3.0		37				239	
21. 6.54		14.0				6.6	4.1	2.5		
1. 7.54		13.7			21					21
20. 7.54	16	12.0	4.2		31				250	
4. 8.54		11.9	3.8	1.9	61				240	18
9. 8.54		12.3	3.9	1.9	36					
13. 8.54		11.4		2.3	52	9.0	5.0	4.0		
17. 8.54		11.1	2.6	2.3	54					
23. 8.54	17	11.2		2.4	50				195	11
31. 8.54		12.5		1.9	59					
2. 9.54		11.3	3.6	1.9						
3. 9.54		10.9	4.1	1.8						
11. 9.54		10.9		1.9	45					
16. 9.54			3.9	1.9	42					
23. 9.54	18	11.9	3.6	2.2	42					
20.10.54	19	12.3	3.8	2.0	54					
30.10.54		11.5	3.9	2.0	49					
8.11.54		10.8	4.1	2.2	50	6.2	4.8	1.4		51
11.11.54		11.1		2.2	61				154	63
15.11.54		11.3	4.1	1.9	64	6.5	4.8	1.7		48
23.11.54	20	11.2	4.4	1.9	45					29
29.11.54		10.9	4.1	2.2	50				127	20
17. 1.55	21	10.4	4.3	1.8	26	6.5	4.8	1.7	149	17
22. 1.55	22	10.7			28					

relationship between serum proteins and calcium or magnesium concentrations (Tables 1, 2, 3).

The electrophoretic patterns of the sera were normal in Cases I and III, but on one examination in Case II during the recovery phase the α_2 globulin was reported raised when the serum calcium was 11.3 mg/100 ml.

Serum cholesterol estimations were not done systematically with changes in treatment. In general, levels were raised during the active stages of the illness and returned to normal with clinical improvement.

Serum alkaline phosphatase estimations were not made frequently enough to draw conclusions. Occasional high values could not be related to any particular phase of treatment.

TABLE 3

Case 3 (P. Ct.).

Date	Age in months	Serum Ca mg%	Serum P mg%	Serum Mg mg%	Blood urea mg%	Proteins g%	Albumin g%	Globulin g%	Cholesterol mg%	Alkaline phosphatase KA units
2.12.52	8	14.4	5.4		88					5
8.12.52					110					
13.12.52		11.2			88					
17. 3.53	11	14.0	6.0		159					23
24. 3.53		10.3			87					
1. 4.53	10								410	
25. 9.53	18	11.7	7.8		100					
29. 9.53		11.7	7.8		46					
26. 2.54	23	13.2	7.1		74				410	5
19. 5.54	25				100	7.3	5.7	1.6		12
3. 6.54	26	13.9	4.9		181				256	
11. 6.54					160					
24. 6.54		12.7	4.9	2.0	136					
4. 7.54	27				152					
17. 7.54		13.3	5.0	2.7	140	5.5	3.9	1.6		
23. 7.54		12.3	3.8	2.3	108				320	
30. 7.54		12.7	2.9	2.3	100					
9. 8.54	28	13.1	4.9	2.3	62					
18. 8.54					160					
23. 8.54		14.1	5.0	2.5	110					
11. 9.54	29	12.5	4.9	2.3	129					
16. 9.54		12.6	3.8	2.6	101					
23. 9.54		12.4	2.7	3.0	61					
20.10.54	30	12.2	3.6	2.5						
25.10.54		12.4	3.7	2.6	85					
8.11.54	31	11.8		2.5	64	6.0	3.7	2.3		15
17.11.54		11.1		2.6	68					16
23.11.54		10.7	2.7	2.8	73					15
29.11.54	32	11.3	2.7	2.4	57					55
17. 1.55	33	11.8	5.0	2.5	80	8.5	5.7	2.8	233	16
1. 2.55	34	12.6	2.3	2.7						
16. 2.55		11.2	1.4	1.9	37					
2. 3.55	36	10.7	3.1	2.3	80	7.7	4.4	3.3		14

Discussion

The investigations undertaken on these three infants with hypercalcaemia must be analysed both from their relation to the particular syndrome and for any light that they may throw on mineral metabolism in general.

The natural history of idiopathic hypercalcaemia in infancy is variable (LIGHTWOOD, PAYNE, STAPLETON and WILKINSON) and one must be cautious in attributing improvements or changes in the condition to any treatments undertaken.

Case I (A. Gd.) had been ill for 6 months before the serum calcium was estimated. Failure to thrive was severe and both the clinical and chemical state improved during one month's treatment with column prepared calcium-free milk. The relapse of the clinical and chemical findings on return to a normal calcium intake indicated that the disease process was still active, and that treatment was effective.

Case II (J. Cl.) had a long history. He was first studied at the age of 16 months. Although his developmental state was retarded, his serum calcium was already approaching normal and his calcium balance was only just positive. It is probable that treatment accelerated, rather than initiated, improvement.

Case III (P. Ct.) was an example of the severest type of hypercalcaemia. Although she improved chemically and radiologically after a prolonged period on a calcium-free diet and several courses of cortisone, her clinical condition, despite recent improvement, remains poor and it seems unlikely that she will recover completely. Her response suggests that early treatment even in the severe grades of hypercalcaemia may result in reversal of the disorder.

The large positive balances of calcium in Case I before treatment is consistent with excessive calcium absorption as they occurred when urine excretions of calcium were high. The smaller positive balances in Case II correspond to a falling serum calcium when the disease process was less active.

Calcium-Free Diets

There is no doubt that calcium-free diets were effective in producing negative calcium balances by faecal loss (Figs. 1, 2) although natural remission may also have played a part in lowering the serum calcium. Two studies on column prepared calcium-free milk demonstrated slightly negative calcium balances. Significantly larger negative balances were obtained on a combination of synthetic calcium-free milk (Trufood) and calcium-free cereal (Glaxo). When whole cow's milk was added to this diet, in both

infants larger negative balances were obtained than with column prepared calcium-free milk alone.

The high inorganic phosphorus and high phytic acid content of calcium-free cereal were probably responsible for binding the calcium of intestinal secretions. Comparison with magnesium and phosphorus balances showed that calcium balances were truly negative, and not due to collection variations. When full diets with no restrictions except Vitamin D were given, calcium balances became positive once more. The balances provided unequivocal evidence that calcium-free diets, especially when cereal was added, were effective in removing calcium in the faeces.

The urine calcium, magnesium and phosphorus excretions changed in different ways during the transition from whole milk to calcium- and magnesium-free column prepared milk. Magnesium excretion decreased gradually whereas urine excretion of calcium almost ceased when serum calcium fell. Without further change in diet, the serum calcium rose slightly and urine calcium excretion was slowly re-established. These changes coincided with an increase in urine phosphorus excretion. Serum magnesium concentration and hence urine magnesium excretion may have been maintained by the comparatively ready availability of intracellular magnesium. A sudden fall in serum calcium from 14.4 mg/100 ml to 11.4 mg/100 ml may have caused an increased output of parathyroid hormone from glands adapted to the higher level, with increased urine phosphorus, rise in serum calcium to 12.9 mg/100 ml and a slow increase in urine calcium.

Cortisone

It is difficult to separate the long-term effects of cortisone from those caused by the calcium-free diets, but the short-term effects were striking. On all occasions falls in serum calcium occurred, in most instances sharply (Fig. 9). Balance studies during cortisone therapy were equivocal (Figs. 1, 2). One infant (Case I) was receiving a calcium-free diet at the same time, whilst the other (Case II) had comparable negative magnesium and phosphorus balances, possibly due to a collection variation. Allowing for these factors, it is probable that cortisone caused slight negative calcium balances, but not to the extent obtained with calcium-free diets. This is consistent with the view that cortisone prevented absorption of calcium by interfering with the action of vitamin D. The falls in serum calcium, however, were more rapid and extensive than with calcium-free diets. As the body weights increased during cortisone therapy, haemodilution may have played a small part in the change in serum levels. Although urine calcium excretions were diminished during the period of the balance studies on cortisone,

these collections were made after cortisone had been given for several days, by which time serum calcium levels had fallen and therefore it is possible that increases in glomerular filtration rates may have led to higher calcium clearances when cortisone was first used. There is no evidence that cortisone causes the deposition of calcium in bone; in fact the reverse may occur. The explanation for the more dramatic effect of cortisone on serum calcium probably lies in a combination of factors, in contrast to the single action of calcium-free diets. This effect of cortisone has been previously observed: in idiopathic hypercalcaemia of infancy (CREERY and NEILL), and in sarcoidosis with hypercalcaemia in adults (SHULMAN, SCHOENRICH and HARVEY, DENT, FLYNN and NABARRO, ANDERSON, DENT, HARPER and PHILPOT, CITRON and SCADDING, HENNEMAN, CARROLL and DEMPSEY).

Renal Function

No formal tests were made, but changes in blood urea and serum phosphorus were probably due to variations in renal function.

Before treatment two infants (Cases I and III) had very high blood urea levels (180 mg/100 ml and 168 mg/100 ml), and at the end of treatment these had fallen (37 mg/100 ml and 50 mg/100 ml). These falls were by no means steady. There were fluctuations of 80–100 mg/100 ml occurring within 1–2 weeks of the institution and withdrawal of either calcium-free milk or cortisone (Figs. 3, 4, 5). These changes were not always accompanied by marked changes in weight, so were not merely due to variations in the state of hydration. The serum phosphorus levels changed in parallel fashion, sharp falls occurring when cortisone was given (Fig. 10). At times concentrations fell from normal to subnormal, even as low as 1.4 and 2.0 mg/100 ml. This effect of cortisone on serum phosphorus has also been noted by DENT *et al.*, CITRON and SCADDING, and CREERY and NEILL. Whether these changes were mainly due to decreased renal tubular absorption (INGBAR, KASS, BURNETT. RELMAN, BURROWS and SISSON) or a transfer of phosphorus across cell boundaries (GEMZELL and SAMUELS) is not known.

High levels of serum calcium are known to cause renal damage which is recognizable histologically, and these changes are sometimes found in cases of idiopathic hypercalcaemia which come to autopsy (LOWE *et al.*, DAWSON and CRAIG): these histological changes can hardly be reversible in 1 or 2 weeks, so it is reasonable to suppose that the changes were earlier or of a different nature. No evidence was obtained to decide whether there was a blocking of the renal tubules (BJØRNEBOE, BRUN, IVERSEN, GORMSEN and RAASCHOU) or a disturbance of the function of the renal tubular cells.

Failure to excrete calcium can hardly have been responsible for the hyper-

calcaemia. Indeed, the close parallel between the serum calcium level and urine calcium excretion suggests that the latter was regulated by the calcium load presented to the kidneys. It is possible, however, that high urine calcium excretions were due to the action of Vitamin D on renal tubular cells (DENT (10), HENNEMAN *et al.*, STAPLETON and EVANS).

Although these studies do not provide any new evidence on the aetiology of idiopathic hypercalcaemia of infancy, the findings support the view that there is a greater response by some infants than by others to small doses of Vitamin D (FOLLIS, PARK and JACKSON, STAPLETON and EVANS, LIGHTWOOD and STAPLETON). It is even possible that the disorder may sometimes start in utero, and be affected by the maternal intake of Vitamin D (FINOLA, TRUMP and GRIMSON).

Preliminary observations on Cases I and II have been reported elsewhere (STAPLETON and EVANS).

We wish to thank Dr. ANDREW BARLOW and Dr. E. C. ALLIBONE respectively for referring Cases II and III, Dr. W. F. J. CUTHBERTSON (Glaxo Laboratories) for supplying calcium-free cereal and calcium-free milk, Trufood for calcium-free milk, and Cow and Gate Laboratories for a full-cream dried milk without added vitamin D. Dr. REGINALD LIGHTWOOD was in charge of the cases and he has given us constant help and encouragement. The majority of the analyses were done in our own laboratory and we particularly wish to thank Mr. I. W. J. EVANS for his work; he also drew the charts. We are grateful to the Department of Chemical Pathology for doing the urea, alkaline phosphatase, cholesterol and protein estimations, and to Drs. W. W. PAYNE and R. H. WILKINSON for the electrophoretic studies of the serum proteins.

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Summary

1. Three cases of idiopathic hypercalcaemia of infancy were studied; the changes in serum chemistry were followed in all three cases and mineral balance studies were made in the two male infants.

2. Calcium-free diets caused a fall in the serum calcium.

3. Calcium-free milks caused a negative calcium balance due to loss of calcium in the faeces. This was greatly increased by the addition of a calcium-free cereal, which had a high phosphorus and a high phytic acid content.

4. Cortisone caused a fall in serum calcium only during the period of its administration.

5. Cortisone caused a slight negative calcium balance.

6. There was evidence that when the serum calcium was lowered, renal function improved.

7. No significant changes were observed in the phosphorus or magnesium balances.

L'hypercalcémie idiopathique chez le nourrisson. Etude du bilan des minéraux.

Trois cas d'hypercalcémie idiopathique de la première enfance ont été étudiés. On a suivi les modifications de la composition chimique du sang et une étude a été faite du bilan des minéraux chez deux nourrissons masculins. Des régimes sans calcium provoquaient un abaissement du calcium sérique. Les laits sans calcium provoquaient un bilan en calcium négatif causé par une déperdition de calcium dans les fèces. Celle-ci était fortement augmentée par l'addition de céréales exemptes de calcium et riches en phosphore et acide phytique. La cortisone faisait baisser le calcium sérique, uniquement pendant la période de son administration; elle rendait aussi le bilan du calcium légèrement négatif. Il semblait que la fonction rénale s'améliorait lorsque le serum calcique diminuait. On n'a pas observé de modifications spéciales dans les bilans du phosphore et du magnésium.

Idiopathische Hypercalkämie im Säuglingsalter. Studien des Mineralgleichgewichts.

Drei Fälle von idiopathischer Hypercalkämie im Säuglingsalter wurden untersucht; die Veränderungen des Serumchemismus wurden in allen drei Fällen verfolgt und bei zwei männlichen Säuglingen wurden Mineralgleichgewichtsstudien gemacht. Calciumfreie Diät bewirkte einen Abfall des Serum-Calciums. Calciumfreie Milch rief eine negative Calcium-Bilanz hervor, bedingt durch einen Verlust an Calcium mit dem Stuhl. Dieses wurde beträchtlich verstärkt durch den Zusatz von calciumfreiem Getreide, das einen hohen Phosphor- und einen hohen Pflanzensäuregehalt hatte. Cortison bewirkte einen Abfall des Serum-Calcium nur während der Zeit seiner Anwendung. Cortison bedingte eine leicht negative Calcium-Bilanz. Es war augenscheinlich, dass sich bei Erniedrigung des Serum-Calcium die Nierenfunktion besserte. Es wurden keine deutlichen Veränderungen in der Phosphor- oder Magnesium-Bilanz beobachtet.

Hipercalcemia idiopática. Estudios del balance mineral.

Se estudiaron tres casos de hipercalcemia idiopática; los cambios en la química sanguínea fueron seguidos en los tres casos y el balance mineral estudiado en los dos de sexo masculino. Se comprobó: que las dietas libres de calcio causaban una caída en el calcio sérico; que las leches sin calcio causaban un balance negativo debido a la pérdida de calcio por las heces. Este era aumentado por la adición de cereal libre de calcio, con alto contenido en fósforo y ácido fítico. La cortisona provocaba una caída del calcio sérico solo durante el período de su administración, provocando además un ligero balance negativo de él. Había evidencia de que al descender el nivel sérico de calcio mejoraba la función renal. No se observaron cambios significativos en los balances de fósforo y magnesio.

References

1. Anderson, J., Dent, C. E., Harper, C. and Philpot, G. R.: Effect of cortisone on calcium metabolism in sarcoidosis with hypercalcaemia; possibly antagonistic actions of cortisone and vitamin D. *Lancet, 2:* 720, 1954.
2. Archer, H. E. and Robb, G. D.: The tolerance of the body for urea in health and disease. *Quart. J. Med., 18:* 274, 1925.
3. Bjørneboe, M., Brun, C., Iversen, P., Gormsen, H. and Raaschou, F.: Two cases of calcinosis renis, studied by means of renal biopsy and renal function tests. *J. Clin. Invest., 31:* 727, 1952.
4. Citron, K. M. and Scadding, J. G.: Sarcoidosis, hypercalcaemia, calcinosis and renal impairment. *Proc. Roy. Soc. Med., 47:* 507, 1954.
5. Creery, R. D. G.: Idiopathic hypercalcaemia of infants. *Lancet, 2:* 17, 1953.
6. Creery, R. D. G. and Neill, D. W.: Idiopathic hypercalcaemia in infants with failure to thrive. *Lancet, 2:* 110, 1954.
7. Dawson, I. M. P. and Craig, W. S.: Nephrocalcinosis and hypercalcaemia in infancy. *Lancet, 1:* 974, 1954.
8. Dent, C. E., Flynn, F. V. and Nabarro, J. D. N.: Hypercalcaemia and impairment of renal function in generalized sarcoidosis. *Brit. M. J., 2:* 808, 1953.
9. Dent, C. E.: Personal communication (1954).
10. —— *In* "The Kidney": Some Aspects of Calcium and Phosphorus. (Ciba Foundation and Renal Association Symposium) p. 242. Churchill, London, 1954.
11. Fanconi, G., Girardet, P., Schlesinger, B., Butler, N. and Black, J.: Chronische Hypercalcämie, combiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Missbildungen. *Helvet. paediat. acta., 7:* 314, 1952.
12. Ferguson, A. W. and McGowan, G. K.: Idiopathic hypercalcaemia of infants: low-calcium treatment. *Lancet, 1:* 1272, 1954.
13. Fiske, C. H. and Subba Row, Y.: The colorimetric determination of phosphorus. *J. Biol. Chem., 66:* 375, 1925.
14. Finola, G. C., Trump, R. A. and Grimson, M.: Bone changes in the fetus following administration of dicalcium-phosphate and viosterol to the pregnant mother. *Am. J. Obst. & Gynec., 34:* 955, 1937.
15. Follis, R. H. (Jr.), Park, E. A. and Jackson, D.: The relationship of Vitamin D administration to the prevalence of rickets observed at autopsy during the first two years of life. *Bull. Johns Hopkins Hosp., 92:* 426, 1953.
16. Garner, R. J.: Colorimetric determination of magnesium in plasma or serum by means of Titan yellow. *Biochem. J., 40:* 828, 1946.
17. Gemzell, C. A. and Samuels, L. T.: The effect of hypophysectomy, adrenalectomy and of ACTH administration on the phosphorus metabolism of rats. *Endocrinology, 47:* 48, 1950.
18. Harris, L. C.: Biochemical changes and osteosclerosis after sulphamezathine therapy in idiopathic hypercalcaemia of infancy. *Arch. Dis. Childhood, 29:* 232, 1954.
19. Harrison, G. A.: Chemical Methods in Clinical Medicine, 3rd. ed., p. 382. Churchill, London, 1947.
20. Henneman, P. H., Carroll, E. L. and Dempsey, E. F.: The mechanism responsible for hypercalcuria in sarcoid. *J. Clin. Invest., 33:* 941, 1954.
21. Ingbar, S. H., Kass, E. H., Burnett, C. H., Relman, A. S., Burrows, B. A. and Sisson, J. H.: The effects of ACTH and cortisone on the renal tubular transport of uric acid, phosphorus and electrolytes in patients with normal renal and adrenal function. *J. Lab. & Clin. Med., 38:* 533, 1951.
22. King, E. J.: The colorimetric determination of phosphorus. *Biochem. J., 26:* 292, 1932.
23. King, E. J. and Armstrong, A. R.: Convenient method for determining serum and bile phosphatase activity. *Canad. M.A.J., 31:* 376, 1934.
24. Lightwood, R.: Idiopathic hypercalcaemia in infants with failure to thrive. *Arch. Dis. Childhood, 27:* 302, 1952.
25. Lightwood, R. and Stapleton, T.: Artificial feeding of infants. *Lancet, 2:* 1230, 1954.
26. Lightwood, R., Payne, W. W., Stapleton, T. and Wilkinson, R. H.: In preparation.
27. Lowe, K. G., Henderson, J. L., Park, W. W. and McGreal, D. A.: The idiopathic hypercalcaemic syndromes of infancy. *Lancet, 2:* 101, 1954.
28. McCance, R. A. and Widdowson, E. M.: Phytin in human nutrition. *Biochem. J., 29:* 2694, 1935.
29. Orange, M. and Rhein, H. C.: Microestimation of magnesium in body fluids. *J. Biol. Chem., 189:* 379, 1951.
30. Payne, W. W.: The blood chemistry in idiopathic hypercalcaemia. *Arch. Dis. Childhood, 27:* 302, 1952.

31. Russell, A., Young W. F., Jacoby, N. M. and Dobbs R. H.: Severe idiopathic infantile hyper calcaemia. Long-term response of 2 cases to low calcium diet. *Proc. Roy. Soc. Med., 47:* 103 1954.
32. Sackett, G. E.: Modification of Bloor's method for the determination of cholesterol in whole bloo or blood serum. *J. Biol. Chem., 64:* 203, 1925.
33. Schlesinger, B., Butler, N. and Black, J.: Idiopathic hypercalcaemia and osteosclerosis. *Maandschr. kindergeneesk., 22:* 293, 1954.
34. Shulman, L. E., Schoenrich, E. H. and Harvey, A. McG.: The effects of adrenocorticotropi hormone (ACTH) and cortisone on sarcoidosis. *Bull. Johns Hopkins Hosp., 91:* 371, 1952.
35. Stanford, R. V. and Wheatley, A. H. M.: The estimation of calcium in blood. *Biochem. J., 19* 710, 1925.
36. Stapleton, T. and Evans, I. W. J.: Idiopathic hypercalcaemia in infancy. *Helvet. pædiat. acta 10:* 149, 1955.
37. Tisdall, F. F. and Kramer, B.: Methods for the direct quantitative determination of sodium potassium, calcium and magnesium in urine and stools. *J. Biol. Chem., 48:* 1, 1921.

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Ist die diätetische Behandlung der Säuglings-Enteritis entbehrlich geworden?

von ERNST FREUDENBERG

Es ist unbestritten, dass sich die Prognose der schweren Enteritis im Säuglingsalter in den letzten Dezennien wesentlich gebessert hat. An diesem Fortschritt sind die parenterale Flüssigkeitstherapie — besonders die endovenöse —, die antibiotischen Behandlungsverfahren und auch die Plasma- oder Bluttransfusion beteiligt. Hingewiesen sei auch auf die Remineralisierung mit Kalium. Fast durchwegs ist anerkannt, dass nach dem Ausgleich der Wasser- und Mineralverluste auch eine diätetische Behandlung stattzufinden hat. Letzterem Punkt wird durch JADRNICEK und MORES in einer in dieser Zeitschrift kürzlich erfolgten Publikation (44: 293, 1955, Literatur dort) widersprochen, indem empfohlen wird, dass im erwähnten Zeitpunkt sogleich mit der Zufuhr von 80 % des calorischen Bedarfes unter folgender rascher Steigerung auf 100 % begonnen werden soll. Im Gegensatz hierzu halten auch in der letzten Zeit erschienene Lehrbücher angesehener Autoren am herkömmlichen Verfahren fest, das die oben genannten Autoren verwerfen. Es seien erwähnt DEBRÉ-LELONG in ihrer „Pédiatrie", HUSLER im LUST-PFAUNDLERschen Lehrbuch, ROHMER in der „Pathologie Infantile" von DEBRÉ-LELONG-ROMER, ELLIS in „Disease in Infancy and Childhood", ROMINGER in seinem Lehrbuch.

Das übliche Verfahren rechnet damit, dass erst nach 8 Tagen eine Zufuhr von 60 % der vollen Ernährung, der sogenannte Erhaltungsbedarf, erreicht wird. Ist es richtig, nach 2–3 Tagen 80 % zu geben? Bedeutet die verminderte Zufuhr während beschränkter Zeit eine Gefährdung im Sinne eines Hungerschadens?

Wenn diese Fragen im Folgenden erörtert werden sollen, kann es sich nicht um eine Kritik der oben zitierten Arbeit handeln, deren summarische Form hierzu nicht die Unterlage bietet. Nur soviel sei gesagt, dass die kurvenmässig wiedergegebenen Fälle von Toxikose das Attribut schwerster Fälle nicht verdienen. Es fehlt höheres Fieber, und die Diarrhöen hören am ersten Tage der Spitalbehandlung schon auf. Letzteres gilt auch für die „Dyspepsia gravis", die kurvenmässig dargestellt ist.

Unter Übergehung der Arbeiten von CHUNG sowie CHUNG und VISCOROVA, auf die wir unten zu sprechen kommen, seien die als Unterstützung der Therapie der raschen oralen Nahrungszufuhr erwähnten Arbeiten kurz besprochen. Die Anführung der spärlichen Fälle, die KEEFE (1948) veröffentlicht hat, besteht m.E. nicht zu Recht. Es handelt sich nicht um Toxikosen. Die Arbeit propagiert die Anwendung von Apfeltrockenpulver. Dass man auf diesem und auf ähnlichem Wege in gegebenen Fällen Gutes erreichen kann, bestreitet wohl niemand, auch dass in vielen dieser Fälle eine nur leichte und zeitlich beschränkte Nahrungsverminderung genügt. Es ist nicht am Platze, wenn hierbei das Gespenst der Hungerhypoproteinämie beim klassischen Vorgehen an die Wand gemalt wird. Wir verweisen einmal auf die eingangs erwähnten Plasma- und Bluttransfusionen und bestreiten im übrigen, dass in 1–2 Wochen eine Hypoproteinämie beim normalen Vorgehen entstehen kann. In der Arbeit von MANN, ROSS, SHEILA und PETERSON (1952) finden sich keine Anhaltspunkte für die Befürwortung rascher oraler Nahrungszufuhr. Am dritten Tage nehmen die Autoren abwechselnde Fütterungen mit stark verdünnten Milchmischungen (1 : 12 evaporierte Milch) und mit Zucker-Elektrolyt-Lösungen vor. Sie empfehlen Plasma intravenös.

Entschiedene Befürworter rascher Realimentation sind dagegen MITCHELL, DONALD und BIRDSONG (1949). Sie waren bei ihren Untersuchungen noch nicht im Besitze kaliumangereicherter Lösungen, und sie begründen ihr Vorgehen teilweise mit der besseren Kaliumzufuhr durch dasselbe. Für die Zukunft erhoffen sie eine weitere Besserung durch Kaliumlösungen. Dies nimmt einer Fortsetzung ihres Vorgehens etwas von seiner Begründung. Ihre Fälle kommen aus einem amerikanischen Südstaat (Virginia), wo noch ein ausgeprägtes, wohl klimatisch bedingtes Sommermaximum für die Säuglingsdiarrhöen besteht, das im nördlichen Europa seit Jahrzehnten verschwunden ist. Wir dürfen annehmen, dass akute Hitzeschäden in diesem Krankengut eine grössere Rolle spielen als Infekte und Nährschäden.

In einigen Punkten kann allen zitierten Autoren voll zugestimmt werden. Sie verwahren sich mit Recht gegen den Gebrauch von Abführmitteln. Sie lehnen die Regel ab, dass so lange intravenös zu ernähren sei, bis 12 oder 24 Stunden lang kein Stuhl erschienen sei. Sie verwahren sich endlich überhaupt gegen die übermässige Ausdehnungsdauer parenteraler Ernährung. Auch hierin stimmen wir ihnen bei.

Beim klassischen Vorgehen wird all das nicht empfohlen. Der Wiederaufbau der Ernährung soll zwar vorsichtig aber ohne skrupulöse Berücksichtigung der Stuhlbeschaffenheit erfolgen.

Es seien nun noch einige allgemeine Gesichtspunkte zu dem berührten Problem der Realimentation entwickelt.

1. In der Medizin gilt ganz allgemein der Grundsatz, dass geschädigte Organe mit einer „functio laesa" geschont werden müssen. Darüber setzt sich die rasche Realimentation hinweg. Hierbei ist man aber nicht einmal konsequent in der Innehaltung des eingeschlagenen Weges. Wenn es keiner Schonung bedarf, dann bedarf es auch keiner besonderen Heilnahrungen, die geschaffen sind, um die Verdauungsfunktionen eben zu entlasten. Warum also noch Buttermilch, Eeiweissmilch, gesäuerte Milchen usw.? Dass man auf mannigfachen Wegen zum Ziele kommt, dass es nicht ganz bestimmte Indikationen für jede einzelne Heilnahrung gibt, ist nicht zu bestreiten. Allen Heilnahrungen liegt aber die Tendenz, die Verdauungsfunktion zu schonen, zu Grunde. Gibt man diese Tendenz auf, so ist es inkonsequent, Heilnahrungen noch zu gebrauchen. Die pädiatrische Arbeit eines Menschenalters kann dann als unnötiger Ballast über Bord geworfen werden.

2. Wir wissen heute, dass zum mindesten ein erheblicher Teil der „akuten Dyspepsien" und „Toxikosen" entzündliche Prozesse sind, Enteritiden, verursacht durch Escherichia-Stämme oder andere Erreger, denen ein pathalogisch-anatomisches Substrat am Darmkanal entspricht (Adam und Froboese 1925). Demgemäss ist es nicht denkbar, dass ein solcher Schaden in 2 Tagen behoben ist, und dass der geschädigte Darm in so kurzer Zeit seine volle Leistungsfähigkeit wiedergewinnt. Vom funktionellen Schaden wissen wir folgendes: Masslow fand schon 1927 bei akuten wie chronischen Ernährungsstörungen verminderte Bildung von Pepsin, Magenlab und Salzsäure. Kritaigorodskaja wies 1931 auf Hypo- und Dyspankreatismus bei Dyspepsie, Colitis, parenteralen Störungen hin. Véghely stellte 1947 gestörte Lipolyse im Magen bei enteralen und parenteralen Erkrankungen fest sowie verzögerte Magenentleerung. Endlich beschrieb Dittrich 1952 Störungen der Motorik, des Tonus, der Sekretion, der Resorption, die er auf röntgenologischem Wege nachwies. Solche Veränderungen konnten nach Heilung einer Dyspepsie noch nach Wochen in abgeschwächter Form gefunden werden. Sie müssen als Grundlage der Recidivbereitschaft nach schweren Störungen betrachtet werden. Diese Tatsachen zeigen, dass anatomische und funktionelle Schäden bei Enteritis am Darmkanal nachgewiesen wurden. Man kann sich nicht über sie hinwegsetzen und nach solchen Erkrankungen rasch voll ernähren.

3. Dem neuen Verfahren wird nachgerühmt, dass es die bei langsamer Realimentation drohende Dystrophie verhüten soll. Mir persönlich sind solche Dystrophien in langen Jahren und bei reichlichem Material unbe-

kannt geblieben. Die Gewichtskurven hatten bei der klassischen Behandlung durchweg aufsteigende Tendenz.

Dem Argument der Dystrophie-Verhütung liegt überhaupt ein Fehlurteil zu Grunde. Die Gewichtsstürze bei akuten Störungen werden bekanntlich durch Wasser- und Salzverluste bedingt, die es auszugleichen gilt. Vom Kalorienmangel drohen keine *akuten* Gefahren, die in 1–2 Wochen eintreten könnten, falls nicht schon eine schwere Dystrophie vorliegt. Dagegen droht bei rascher Realimentation eine andere Gefahr, auf die DARROW bei seiner ablehnenden Kritik des Verfahrens von CHUNG hingewiesen hat mit den Worten „larger intakes resulted in increased stool volumes". Dies wurde durch CHUNG zugegeben. Solche voluminösen Stühle sind wasser- und mineralreich. Es werden deshalb bei dem neuen Verfahren in der Nachbehandlung immer wieder Infusionen nötig. Es besteht einfach eine kaschierte Diarrhöe weiter, etwa wie bei Coeliakie und Pankreasfibrose, wo auch ohne vermehrte Stuhlzahl eine chronische Störung der Wasserbindung vorliegen kann, solange die Darmvorgänge nicht normalisiert sind. Diesen Tatbestand muss man im Auge behalten, wenn von der Seltenheit von „Recidiven" beim neuen Vorgehen die Rede ist.

Zusammenfassung

Die rasche Realimentation nach schweren Enteritiden verstösst gegen den allgemeinen, medizinischen Grundsatz, dass ein geschädigtes Organ geschont werden muss. Es wird auf die nachgewiesenen anatomischen und funktionellen Schäden hingewiesen. Die rasche Realimentation führt zu voluminösen Stühlen, was man als eine kaschierte Diarrhöe mit weiter gefährdetem Wasser- und Mineralhaushalt bezeichnen kann. Das Verfahren wird abgelehnt. Marasmus und Hypoproteinämie entwickeln sich nicht bei korrektem Gebrauch der klassischen Methode.

Is the dietetic treatment of infantile diarrhea no longer necessary?

Early oral feeding with high caloric intake after severe infantile diarrhea is no safe treatment. Anatomical and functional lesions of the intestinal canal have been found in cases of severe diarrhea. Early oral feeding may result in bulky stools, deteriorating water and mineral balances. This method is to be rejected. Emaciation and hypoproteinemia do not result from the usual treatment if mistakes and exaggerations are avoided.

Le traitement diététique de la diarrhée du nourrisson est-il devenu superflu?

La réalimentation rapide à la suite de graves entérites est en opposition avec le principe généralement admis en médecine, selon lequel tout organe lésé doit être ménagé. Les altérations anatomiques et fonctionelles au niveau du tractus digestif dans le cas de diarrhée grave sont bien connues. La réalimentation rapide provoque des selles volumineuses, qui en masquant une diarrhée augmentent les troubles du métabolisme de l'eau et des substances minérales. Ce procédé doit être abandonné. Il ne résulte de la méthode habituelle appliquée selon les règles de l'art ni hypoprotéinémie ni marasme.

¿Se ha hecho innecesario el tratamiento dietético de las diarreas del lactante?

La realimentación rápida después de graves enteritis se opone al principio de dejar en reposo un órgano lesionado. Son bien conocidas las alteraciones anatómicas y funcionales a nivel del tracto digestivo como consecuencia de diarreas graves. La realimentación rápida provoca deposiciones voluminosas que, enmascarando una diarrea, aumentan los trastornos del metabolismo acuoso y mineral. Dicho procedimiento debe ser abandonado. El método habitual, aplicado según las reglas del arte, no produce ni hipoproteinemia ni marasmo.

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Kinderklinik
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CASE REPORT

Skin Infection with Salmonella Rostock in a Newborn Infant

by ROLF LUNDSTRÖM

From Epidemisjukhuset, Stockholm
(Heads: J. Ström, M.D. and J. Lindahl, M.D.)

Judging by the few accounts in the literature, skin infections caused by Salmonella organisms are extremely rare. In each of two earlier reports, the infection was contracted by a veterinary surgeon who had delivered a sick animal.

FUJIMURA and HOSHI, in Japan, described boils which appeared on one arm of a veterinary surgeon on the day after he had delivered a mare with paratyphoid fever, caused by *S. abortus equi*. Both this organism and staphylococci were isolated from the boils. In the case reported by HENIG, a veterinary surgeon had pustules on both forearms. He had assisted at a premature calving. The calf was emphysematous, and the cow—which was slaughtered—was found to have metritis. Four days later, an eruption appeared on the veterinarian's forearms, which had been in intimate contact with the birth canal of the sick cow. After a further two to three days, follicular pustules, the size of a pinhead, developed. There was also swelling of the regional lymph nodes, which were tender. Penicillin therapy for three days resulted in no improvement. On the 11th day after he had delivered the animal, the content of the pustules was examined. In addition to leukocytes, short, gram-negative rods were found. Culture showed them to be Salmonella organisms, later classified by HIRSCH *et al.* as a new type denoted as *S. emek*, with the antigenic formula (VIII), XX:g,m,s: –. In the discussion of the case, HENIG pointed out that there might primarily have been a mixed infection with staphylococci or streptococci which could not be demonstrated later, owing to penicillin therapy.

In this connexion, the following case seems to be of interest.

Case Report

A. J., a 29-year-old secundipara, was admitted to the maternity department of Södersjukhuset on the day after the onset of fever, nausea and diarrhoea. Labour pains started concurrently. On admission, her temperature was 38.5°C. She was placed in an isolation room, and gave birth to a full-term girl on the same day. On the following day, she had about 20 watery, non-fetid defaecations; the faeces gradually became firmer in consistency and of normal frequency.

Bacteriologic culture of the faeces showed the presence of Salmonella organisms.

The patient was therefore transferred, together with her child, to Epidemisjukhuset on the seventh day after delivery. Physical examination on admission showed nothing abnormal, and nothing pathologic was found in the urine. There was slight leukocytopenia, with 3,800 W.B.C. per cu. mm; 69 per cent leukocytes, 1 per cent monocytes and 30 per cent lymphocytes. Widal's test was negative in a blood sample taken on the 9th day of the illness. Culture of the faeces showed a growth of *S. rostock*[1] in three samples during the first two weeks, when her temperature was subfebrile.

Three cultures were made of the breast milk, each time with negative results. The patient was discharged from hospital after five weeks; four negative cultures of the faeces had then been obtained at 4-day intervals.

M. J., the child, weighed 3,600 g at birth. In the maternity department she was isolated from the other infants, but was breast fed by her mother. On the day after birth her weight was 3,490 g and on the 5th and 7th day, respectively, it was 3,360 g. While in the maternity department, her temperature was normal. During the last few days there, a few eruptions were seen in the axillae; they were interpreted as pemphigus neonatorum. She had a few loose defaecations on the last day.

On admission to Epidemisjukhuset on the 7th day of life, her weight was 3,360 g and her temperature slightly subnormal (35.5°C). The general condition was good. The skin was faintly icteric and the throat was slightly red and swollen. In each axillae there were a few slightly elevated, round, yellowish-grey vesicles about 4 mm in diameter, surrounded by a small, reddened zone. Physical examination showed otherwise normal conditions.

Culture of the cloudy, yellowish-grey, purulent content of the vesicles showed the presence of staphylococci with a negative reaction to the coagulase and mannitol test, as well as a sparse growth of *S. rostock*. The latter organism was also recovered from the faeces.

During her stay in Epidemisjukhuset, the infant was neither looked after nor nursed by her mother. She was given the mother's milk in a bottle, 350 g per day on the first few days, increased gradually to 650 g per day. Her weight reached the lowest level, 3,170 g, at the end of the second week of life; thereafter she gained satisfactorily, and weighed 4,740 g at three months.

During the first week in Epidemisjukhuset, she had 2–4 loose, mucous defaecations per day, and on a few occasions during the second week (3rd week of life) vomited slightly. The skin lesions dried up in a few days and healed without antibiotic therapy. The subsequent course was uneventful; defaecation was normal and the child developed normally. *S. rostock* was recovered repeatedly from the faeces during the first eight weeks in hospital. She was discharged at 13 weeks of age (6 weeks after her mother); four negative cultures had then been obtained from the faeces.

Discussion

During the neonatal period, Salmonella infections are usually caused by faecal contamination from the mother, even if intrauterine transmission is possible. SCHMIDT was able to isolate the paratyphoid B bacillus from a

[1] The bacteriological examinations and typing of the Salmonella strains were performed at the Municipal Bacteriological Laboratory, Stockholm.

blood sample taken immediately after birth from a child whose mother had paratyphoid fever. The same organism was subsequently recovered from the child's faeces.

Pemphigus neonatorum is generally caused by *Staph. pyogenes*, but streptococci may also be responsible.

In the case described in this paper, coagulase and mannitol-negative staphylococci, as well as *S. rostock*, were present in the content of the vesicles. The latter organism was the cause of the mother's illness, and was repeatedly isolated during eight weeks from the faeces of the child, who also showed clinical signs of a Salmonella infection with diarrhoea, although of mild degree. Consequently, it appears probable that the Salmonella organisms found contributed to the child's pyoderma, which resembled pemphigus neonatorum.

On taking the samples, the possibility of contamination by bacteria on the skin was borne in mind, and the greatest care was taken. Even if it cannot be ruled out with certainty that, despite these precautions, the Salmonella organisms derived from possible faecal contamination of the skin, this seems unlikely. The child was delivered at the peak of the mother's illness, and its skin thus came into the closest possible contact with infective matter; particularly favourable conditions for a skin infection therefore existed.

In the two cases of pyoderma with findings of Salmonella organisms reported earlier, a mixed infection was demonstrated in one of them. In the other, it was not possible to rule out the eventuality of an initial mixed infection, in which the staphylococci or streptococci originally present could have been eliminated by penicillin therapy. It is conceivable that a Salmonella pyoderma cannot develop without the simultaneous presence of staphylococci or streptococci. It is remarkable that in the two earlier cases there was intimate contact with the birth canal of a sick animal, and that in the present case the infection was also associated with delivery.

From the epidemiologic standpoint, the present case is important in view of the considerable role played by bacterial skin infections in the spreading of airborne infections. This has, for example, been demonstrated in the case of streptococcal infections by Loosli *et al.* The greatest caution should therefore be observed in cases of pyoderma in maternity hospitals. This applies in particular when infectious gastro-intestinal disorders occur. There is then reason to bear in mind the eventuality of Salmonella organisms as the possible or, at any rate, as the contributory cause of the skin infection.

Summary

An account is given of pyoderma, resembling pemphigus neonatorum, in a 1-week-old infant suffering from paratyphoid fever. Before and during delivery, the mother had marked symptoms and signs of enteritis. *Salmonella rostock* was isolated from the faeces of both the mother and child. Both staphylococci of apathogenic type and *S. rostock* were recovered from the content of the child's vesicles.

Infection cutanée par le Salmonella rostock chez un nouveau-né.

L'auteur rapporte le cas d'un nourrisson âgé d'une semaine atteint de fièvre paratyphoide et présentant une pyodermie, qui ressemblait au pemphigus du nouveau-né. Avant et pendant l'accouchement la mère présentait des symptomes et des signes d'entérite. Le *Salmonella rostock* a été isolé des fèces de la mère et de l'enfant. On a découvert dans le contenu des vésicules de l'enfant des staphylocoques non-pathogènes et le *Salmonella rostock*.

Hautinfektion mit Salmonella rostock bei einem Neugeborenen.

Es wird von einer Pyodermie, die einem Pemphigus neonatorum ähnelte, bei einem an Paratyphus leidenden, eine Woche alten Kind berichtet. Vor und während der Entbindung hatte die Mutter ausgesprochene Symtome und Zeichen einer Enteritis. Im Stuhl der Mutter und des Kindes wurde *Salmonella rostock* gezüchtet. Staphylokokken von apathogenem Typ sowie *S. rostock* wurden in dem Inhalt der Hautblasen des Kindes gefunden.

Infeccion dermica a Salmonella rostock en un recién nacido.

Se dá cuenta de una piodermia semejando pénfigo neonatorum en un lactante de una semana de edad afecto de fiebre paratifoidea. Antes y durante el parto, la madre tuvo una grave enteritis. Se aisló la *Salmonella rostock* en las deposiciones se madre e hijo. De las vesículas dérmicas del niño se aisló un estafilococo apatógeno y de *S. rostock*.

References

Fujimura, S. and Hoshi, T.: A case of infection with the Bac. abortus equi in man. J. Jap. Soc. vet. Sci. *15:* 159, 1936. Cit. Kauffmann, F., Die Bakteriologie der Salmonellagruppe. Copenhagen 1941.

Henig, E.: Pyodermia caused by Salmonella. Harefuah (J. Med. Assoc. Israel) *37:* 1, 1949.

Hirsch, W., Henig, E. and Sapiro, R.: A new Salmonella type: Salmonella emek. J. Bacteriol. *60:* 213, 1950.

Loosli, C. G., Smith, M. H. D., Cline, J. and Nelson, L.: The transmission of hemolytic streptococcal infections in infant wards with special reference to skin dispersers. J. Lab. & Clin. Med. *36:* 342, 1950.

Schmidt, P.: Ein Fall intrauteriner Übertragung von Paratyfus. D. med. Welt 1915. Cit. Braun, H. und Hofmeier, K., Die congenitale Übertragung der Infektionskrankheiten, *in* Handbuch d. pathog. Mikroorganismen. Jena, Berlin and Wien, I: 1, pp. 523–564, 1929.

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SUMMARY OF SUPPLEMENTS

Studies on Serum Lipids and Lipoproteins in Infancy and Childhood

by STURE RAFSTEDT

Acta Pædiatrica, Supplement 102

In an investigation of the serum lipoproteins in infancy and childhood, in which attention was also directed to the total lipids, total and free cholesterol and phospholipids, and in which use was made of micromethods permitting the performance of all these analyses on 0.6 ml serum and thus even on newborn premature infants, the following observations of interest were made.

In serum from umbilical cord blood the total lipid, the total and free cholesterol and the phospholipid levels were much lower than in serum from normal adults.

In serum from umbilical cord blood the α-lipoproteins represented about 43 per cent and the β-lipoproteins about 33 per cent of the total lipids, as against 30 per cent and 50 per cent respectively in normal adults.

During the first 12 hours of life the total lipids, total and free cholesterol and phospholipids increased by about 10–15 per cent, an increase possibly due to a dehydration of the blood during the first postnatal hours, during which no changes occur in the lipoprotein distribution.

During the first few days of life all the serum lipids increased steadily and on the fourth day they reached levels 80 to 90 per cent higher than at birth.

During the first few days of life the increase in the serum lipids was accompanied not only by an absolute increase in the lipoprotein fractions, especially of the β-lipoproteins (more than 100 per cent), but also by a marked change in the ratio between the α- and β-lipoproteins, the α-lipoproteins on the fourth day representing 29 per cent and the β-lipoproteins 46 per cent of the total lipids, a distribution corresponding roughly to that found in normal adults, in whom, however, the serum lipid levels are higher.

The ratio of the combined to free cholesterol in serum from umbilical cord blood (1.3 to 2.3) was below the normal adult range (2.3 to 3.1) and remained so during the first few days of life, when the combined and the free cholesterol increased in absolute amount.

The cholesterol-phospholipid quotient in serum from umbilical cord blood was about 0.60 and increased to about 0.65 during the first few days of life (normal adult quotient: about 0.90).

The values found for newborn infants delivered by Caesarian section did not differ from those found for infants delivered by the normal route.

After the first few days of life successive analyses of specimens from the same infants during the rest of the first year of life showed that the values for serum lipids and lipoproteins fluctuated with a slight tendency to increase toward the end of the first year.

The ratio of the combined to free cholesterol also showed an increase towards the end of the first year to approach that for normal adults, the cholesterol-phospholipids quotient for the first year being on the average 0.70 and thus lower than in normal adults.

In children (2–14 years) the serum lipids and lipoproteins were higher than for the infants and fell within the adult range.

The ratio of the combined to free cholesterol and the ratio of the total cholesterol to phospholipids were higher for the children than for the infants and approach those for normal adults.

Serum lipids and lipoproteins in umbilical cord blood from premature infants were not found to differ from those found in fullterm infants. However, the serum lipids and lipoproteins did not increase so fast as in fullterm infants, but after about the first month of life no difference was demonstrable between the serum lipid and lipoprotein levels of the premature and fullterm infants.

Enzygotic as well as dizygotic twins of one and the same pair did not differ with respect to the serum lipid and lipoprotein levels of umbilical cord blood, but differences were found between blood samples collected a few days after birth.

In infants on a fat-poor diet as well as in those on a synthetic diet consisting of carbohydrates and proteins the serum lipids and lipoproteins did not increase so much during the first few days of life as in infants on an ordinary diet. The changes in the relative lipoprotein distribution were not so marked as in infants on an ordinary diet.

In newborns fed on carbohydrates only, the serum lipids did not increase, nor did any change occur in the relative lipoprotein distribution during the first few days of life, but as soon as the infants received an ordinary diet, the serum lipids and lipoproteins rapidly reached values found in newborns brought up on an ordinary diet from birth.

Implications of Agenesis of the Spleen on the Pathogenesis of Conotruncus Anomalies in Childhood

by BIÖRN IVEMARK

Acta Pædiatrica, Supplement 104

Six embryos measuring 9–12 mm in greatest length have been shown by the writer to contain early splenic primordia in the left aspect of the dorsal mesogastrium. Their ovulation age is estimated to be 31–36 days. Temporal relations of splenic formation to cono-truncus septation and division of the A–V canal have been discussed. This last is divided before septation of the cono-truncus is completed. The author has shown that early splenic primordia exist at the time of fusion of the A–V canal cushions. At the same time there is initiation of pulmonary lobation, and there is a primitive gut mesentery.

Congenital absence of the spleen (asplenia) is rare. At the Boston Children's Hospital it was found 12 times in an autopsy series comprising 7032 post-mortem examinations. Eleven of them were associated with congenital malformations of the heart and great vessels. Asplenia associated with malformations may be said to constitute a syndrome. It is suggested by the writer that it be called "asplenia, a teratologic syndrome of visceral symmetry".

Data on autopsy cases of asplenia associated with congenital cardiovascular anomalies have been compiled in this study. Such a selection has been made in order to pick up cases of hearts whose formation may be assumed to have gone astray at approximately the same time, that is, when the spleen should have been formed during embryonic life.

Fourteen new cases of this syndrome are reported, and 55 cases have been collected from the literature. Cono-truncus anomalies occur in 65 of 67 cases of asplenia (97 per cent). There are three types. Type A, persistent truncus arteriosus, contains 10 cases; Type B, pulmonary stenosis or atresia, comprises 41 cases (19 with stenosis and 22 with atresia); Type C, transposition of the great arteries without pulmonary stenosis or atresia, 14 cases. There are two cases, Type D, with normal cono-truncus regions, and two cases without available descriptions of this region. In Type A, four of the cases are the writer's; in Type B, seven (four with stenosis and three with atresia) and in Type C, three cases.

The atrio-ventricular region is abnormal in 56 of 58 cases with adequate description (97 per cent). These anomalies vary in type; a common A–V ostium is present in 46 cases, or in 79 per cent. Moreover, there are cases of tricuspid atresia or mitral atresia. The two cases with normal cono-truncus had normal A–V regions.

The cardiovascular anomalies are looked upon as due to developmental arrest. Thus, there are 32 cases of cor biloculare, and 18 additional cases have defects in the area of the ostium primum. In 36 cases there are anomalous pulmonary venous connections, total or partial. In 19 cases there are bilateral superior venae cavae. A new classification of this anomaly is proposed. In 46 instances there is abnormal lobation of the lungs; in 40 of these the lobation is symmetric; and in 35, each lung had three lobes. The liver is transposed in 17 cases and symmetric in 31 cases. The stomach is transposed in 33 instances. There is a common mesentery in 33 cases.

Serious infections occurred in a number of cases. They were more common under the age of 10 months. Five instances of meningitis are present in 66 cases of asplenia, including one case without cardiovascular anomalies. These facts are discussed briefly in relation to the occurrence of infections reported after splenectomy in infancy. The incidence of meningitis in congenital heart disease associated with asplenia does not appear to be significantly higher than in such cases with spleens.

Multiple spleens or rudimentary spleens may occur together with cardiovascular anomalies similar to those encountered in cases of asplenia. Four new cases of this association are reported, and six examples from the literature are mentioned. One additional case of multiple spleens without cardiovascular anomalies is reported. The significance of multiple spleens and the possibility that this defect occurred later in embryogenesis than asplenia are discussed. The associated cardio-vascular anomalies furnish some support for this possibility. Accessory livers were found by the author in two cases of asplenia. The possibility of confusing an accessory liver with a rudimentary spleen is stressed and discussed.

The pathogenesis of the cono-truncus anomalies in cases of asplenia is discussed. There is a statistically significant linkage between the cono-truncus and the A–V region in the present material. All cases with A–V anomalies have malformed cono-truncus regions. All cases with cono-truncus anomalies and adequate description of the A–V regions have malformations of the latter. Two cases with normal cono-truncus have normal A–V regions.

The interrelationship between the cono-truncus and the A–V region is discussed. There is an unusually high incidence (97 per cent) of abnormal A–V region in linkage with an abnormal cono-truncus region. There is evidence that the A–V canal cushions fuse before the septation of the cono-

truncus is complete. This fusion occurs when the spleen is in its early formative stage. The spleen is congenitally absent in all cases. In view of these facts it is concluded that the abnormal A–V region in the cases presented might have been primary to the coexistent cono-truncus anomalies. Clinically, cases of Type B may mimic an uncomplicated tetralogy of Fallot. Attempts at surgical anastomoses failed in four cases in this category. This was presumably due to the severe associated defects, and to the pulmonary arteries' being hypoplastic. Minor surgical procedures have caused death in three instances: one after incision of an atretic anus, another after adenoidectomy, and a third after tonsillectomy. Most of the cases fall within the age range of birth to 1 year. Roentgenologic examination of the abdomen to establish the position of the stomach, the shape of the liver and a possible asplenia should aid in the diagnosis of this syndrome.

The etiology of asplenia, a teratologic syndrome of visceral symmetry, has not been discussed. The cases presented do not furnish data for such a discussion.

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The Pediatric Society of South Sweden

Meeting, May 8, 1955

I. B. Thurell and S. Winblad: **Middlebrook-Dubos' test in tuberculous mothers and their children.**

As has been previously shown, infants of tuberculous mothers become tuberculin-positive after BCG-vaccination much later than children of healthy mothers. It is conceivable that antibodies transmitted from the mother to the child delay the tuberculin positivity. In order to elucidate this problem we have carried out antibody titrations on tuberculous mothers and their newborns (umbilical cord blood) since January 1954. We have employed the agglutination method according to Middlebrook and Dubos as well as the method of hemolysis according to Middlebrook and Fisher. A titer of at least 1 : 8 in the two reactions was required for a positive result. A total of 42 women and their 42 infants were examined. Of the mothers 24 had positive reactions in both tests; of the children of these mothers 3 had positive reactions in both, and 14 had a positive hemolysis reaction. The other mothers and babies had negative reactions. Thus antibodies can be demonstrated in newborn infants of tuberculous women but considerably less often than in the mothers. Furthermore, it is shown that the hemolysis reaction is more easily transmitted to the child's blood than the agglutination reaction.

The results become difficult to evaluate, however, in view of the findings from a simultaneous investigation of nontuberculous control cases comprising 63 women and their 63 infants. Of the mothers 29 had positive reactions; in the children of these mothers no instance of transmitted agglutination reaction could be demonstrated, but there were 6 cases with a positive hemolysis reaction.

The extent to which our findings can contribute to the question of whether the humoral immune bodies neutralize the BCG-infection resulting in delayed tuberculin positivity is, however, extremely uncertain. Further investigations including methods for measuring tissue immunity are required for a more definite answer to this problem.

Tom Reinand: **Familial, congenital, hematogenic cyanosis.**

In three generations of a Gothenburg family there have occurred five cases of congenital, probably predominantly hereditary cyanosis. The cyanosis does not appear to affect the state of health of the members of the family and they do not exhibit any obvious signs of morbidity. Examination of one of them revealed an abnormal non-oxygen carrying blood pigment comprising 20 per cent of the total amount of hemoglobin. In spite of the clinical similarity to congenital methemoglobinemia no elevation of the oxygen capacity was obtained on the addition of methylene blue. The abnormal blood pigment also had an absorption spectrum which deviated from that of methemoglobin and sulfhemoglobin. It did not react on the addition of cyanide and

fluoride and could neither be changed over to methemoglobin by means of ferricyanide nor converted to carboxyhemoglobin. The work of identification of this new blood pigment is still in progress. (A detailed report will be published in *Acta pædiatrica.*)

A. Prag: **Juvenile tuberculosis in Karlskrona 1930—1954.**

Karlskrona is topographically unique as a city in that it is composed of islands without rural districts. The inhabitants are divided into rather strictly defined social classes. Since 1906 the city has had a child welfare centre and in 1914 a tuberculosis dispensary was started. In Karlskrona there used to be a corps of naval cadets with a boarding school for boys from 14 to 17 years of age. In a class of 100 boys who entered in 1930 approximately 50 per cent were tuberculin-positive. After one year about 100 per cent had been infected. Eleven developed tertiary tuberculosis and 5 were dropped for tuberculosis within 3 years. After sanitation improved there was no increase in the tuberculin positivity in the class of 1935. Blekinge has fallen behind the other parts of our country in regard to mortality from tuberculosis. An investigation in 1946 among elementary school children in Blekinge revealed that a higher mortality and morbidity from tuberculosis was associated with low-standard housing conditions and malnutrition.

An $8^1/_2$-year-old boy became ill in the beginning of the nineteen thirties with miliary lesions. These healed and 5 years later there was abundant calcification in both lungs. In 1952 he was still completely well.

Ivar Nilsby: **Meconium peritonitis.**

In this case the family history was non-contributory. The patient was the eighth child, a twin. Both infants had normal birth weight and the delivery itself was without complications. During the first hours after birth the child did not exhibit any symptoms, but after 24 hours, when feeding was begun, he vomited intensively. The abdomen became increasingly distended but it was soft and apparently not tender. Meconium was passed normally. The child showed increasing apathy. There was no fever but an abnormally low temperature. Atresia was suspected and a tube was introduced which passed easily into the duodenum, as shown by bile-colored secretion obtained on suction. Roentgen examination revealed that the abdomen was filled with large amounts of gas and liquid. The child died at the age of 48 hours, 24 hours after the onset of symptoms. The post-mortem examination showed that the abdominal cavity contained considerable air and a turbid, slightly foul-smelling fluid. All the intestines formed a coherent mass with numerous fibrous deposits between the intestinal loops. In the cecal pole there was a hole, one millimeter in diameter, through which meconium could be expressed. Microscopically there was no change in the intestinal wall. The intestinal contents were noticeably thick and viscous compared with normal meconium and contained many macroscopically observable filaments of considerable length. For this reason pancreatic fibrosis may have been a possible etiologic factor.

Acta Pædiatrica 44: 595—597. Nov. 1955

BOOK REVIEWS

H. H. van Gelderen: Pree-school Child Mortality in the Netherlands.

Leiden, H. E. Stenfert Kroese N. V. 1955.

By pre-school children is meant children 1–4 years of age. In the Netherlands these children comprise about 10 per cent of the total population. The death-rate of pre-school children has declined more than that of infants and older children, although there is no organized care for them. The experience gained under very unfavourable conditions (during the World War) has shown that the mortality of the pre-school group of children is more difficult to keep under control than that of infants. The mortality of pre-school boys is higher than that of girls (118 : 100), even if the mortality due to accidents is disregarded (104 : 100). Since 1910 the mortality is higher in the country than in the towns. If death from accidents is excluded, the mortality in rural and urban districts is the same. Different causes of death are discussed. Mortality from infectious diseases has decreased considerably, perhaps most pronounced in tuberculosis. There is no increase of cases of leukemia. During the 1914–18 World War, the Netherlands was neutral, there was no increase of the number of accidents, but during the Second World War, when the country was involved, there was far greater disorganization of social life which led to less care for the children with a marked rise of the number of fatal accidents. A special chapter is devoted to accidents, the most frequent causes being drowning (42 %), traffic accidents (30 %), and burns (10 %). A study of the relations between the mortality rate and the economic conditions of the family did not show any manifest influence of economic factors. The author maintains that pre-school age mortality is a more sensitive criterion of social and hygienic conditions than is infant mortality. This thesis is supported by the fact that the mortality of 1–4-year-old children has fallen more markedly than that of any other age group; that this decline started earlier than the fall in infant mortality; and that the pre-school age mortality curves show higher peaks during the war years.

Peter Heinz Koecher: Klinische Diagnostik für den Kinderarzt.

Ferdinand Enke, Stuttgart, 1955. Price DM 22.20.

The author is head of the Waldörfer Children's hospital, Hamburg-Duvenstedt. He was formerly assistant to Prof. Erich Rominger, who also suggested the preparation of this book. It contains almost all the laboratory methods and tests used in the present pediatric practice, their performance and sources of error, their clinical significance and reliability, their values in different age-groups and the range of variation. For the inexperienced physician the author has compiled a series of tables to help him in the use of the described methods of examination for the differential diagnosis of certain groups of diseases. There may be, quite naturally, different opinions about the evaluation of some methods described, but the author has succeeded fairly well in his choice and judgment. The same applies to the chapter on methods in cardiovascular examinations, written by Dr. H. W. Kirchhoff. The volume is handy to use and can be recommended as an excellent reference book.

***Jörn Gleiss:* Biologische und soziale Faktoren bei der Genese der Frühgeburt.**

Ferdinand Enke, Stuttgart, 1955. Price DM 12.80.

This study is based upon an interview of the parents of 168 premature infants constituting all the prematures born between November 1950 to November 1952, who were admitted to the Medizinische Akademie in Düsseldorf. The interview especially took into consideration the conditions regarding the social environment, pregnancy and parturition, and its aim was to get adequate information about the causes of the premature birth. It was found that only in a minority of cases was evident disease of the mother the cause of the premature birth. Sexual intercourse during the last part of the pregnancy was a less frequent cause than the social situation of the mother. The ratio illegitimate/legitimate pregnancies was twice as great in prematurely delivered mothers as in the female population at large. House-maid was the most frequent profession among the unmarried mothers of premature infants. Only one third of them had continued working until the day of delivery. One seventh of the mothers regarded overwork and exhaustion as the cause of the premature birth. One third of the urban unmarried mothers of premature infants had tried to provoke abortion in order to solve the social conflicts produced by the pregnancy. In the rural districts this happened less frequently. The newborn premature infants, especially those whose mothers were of low social class, should be taken care of in well equipped premature wards headed by pediatricians. The supervision and the welfare of premature babies discharged from the hospital is of importance for the normal development of these children. Prevention of sexual intercourse among unmarried young girls by means of sexual-pedagogic information is one of the most important prophylactic measures against premature birth. Social politics should aim at the protection and conservation of the family.

***I. Müller-Gies and Chr. Lichtenberg:* Atemübungen mit Kindern.**

Georg Thieme, Stuttgart, 1955, 32 pages. Price DM 3.90.

Breathing exercises in children are of great therapeutic importance in certain diseases, specially in asthma. The book in question is instructive and clear and includes only simple exercises. It is chiefly composed of photographic material with a well balanced text. The increasing difficulty of the series of excercises is correct. It is good to see that such a pleasant occupation as playing wind instruments is stressed, and also that swimming is especially emphasized as a good breathing exercise. Similar instruction of the same good quality should be available in every country to help nurses and parents.

Sven Kraepelien

***Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B.:* Diagnosis of Congenital Heart Disease.**

The Year Book Publishers, Chicago, 1955. $22.00.

This book is based on clinical, physiologic and roentgenologic studies of 396 cases of congenital heart disease, performed at the Pediatric Clinic of Karolinska Sjukhuset, Stockholm, by a team consisting of two cardiologists and two roentgenologists. An account is given of the results obtained with the diagnostic methods in use, i.e., physical examination, electrocardiography, phonocardiography, X-ray, electrokymography,

heart catheterization and angiocardiography. Since the two last-mentioned methods have been used extensively and whenever indicated (this has not been done, for instance, in typical cases of patent ductus arteriosus), it has been possible in practically all instances to get a detailed functional and anatomic diagnosis. In this way the authors have been able to appraise the value and the limitations of the different diagnostic means. Furthermore, the evaluation of the physical findings has been greatly facilitated. This is the main contribution in this important work.

The book begins with surveys of the embryologic development, the roentgenologic anatomy and physiology of the heart, especially such details and features that are considered to be important for the angiocardiographic interpretation. Next, a description is given of the technique used. It is stressed that many blood samples should be taken from each chamber. These requirements are fullfilled by the hemoreflector designed by Brinkman (Kipp & Zonen, Delft, Holland). The angiocardiographic apparatus used is a roll-film serial changer taking films in two planes at right angles, with a rate of exposure varying from 12 per sec. to 1 every 10 sec. (Elema-Järnh. Stockholm). Selective angiocardiography was made in 331 cases and venous angiocardiography in 13 cases only.

The authors have classified their cases according to the anatomy of the malformations; those with combined anomalies have been accounted for under the malformation that was considered to be the most important from a functional point of view. Most cases were referred from other pediatric clinics; consequently, operable cases are over-represented. In addition, a number of adult patients were sent from various medical clinics for X-ray and angiocardiography only. On the other hand, such common malformations in early infancy as transposition of the great vessels and "infantile type" of coarctation of the aorta are under-represented. Nevertheless, the authors have been able to investigate not so few cases of such rather uncommon malformations as Ebsteins anomaly, complete anomalous drainage of the pulmonary veins, tricuspid stenosis (earlier not diagnosed *in vivo*), mitral atresia and mitral insufficiency (not described before). Complicated cases like these are accounted for in more detail; otherwise, there are few case reports. The book contains many new observations and concepts; e.g. the effect of pressure loss of velocity in large left-to-right shunts, simulating pulmonary stenosis: the phonocardiographic characteristics of valvular and infundibular pulmonary stenosis, respectively; the possibility of distinguishing between atrial septal defect and simple patent foramen ovale by means of a baloon catheter; the impossibility to differentiate valvular from sub-valvular aortic stenosis by means of the second aortic sound or arterial pulse curves.

The co-operation between the authors seems to have been so nearly perfect as possible, and the reader is easily referred from the one section of a chapter to the other. The illustrations, mainly X-ray and angiocardiographic pictures, are numerous and of good quality. Among the many references the reader will recognize most of the best articles written in this field.

This book may be most warmly recommeded to all cardiologists and roentgenologists dealing with diagnostics of congenital heart disease.

LARS ERIK CARLGREN, Gothenburg, Sweden.

Acta Pædiatrica **44**: 598 Nov. 1955

ANNOUNCEMENTS

Second European Congress of Cardiology

The European Society of Cardiology, which arranges the European congresses of Cardiology, has entrusted the Swedish Society of Cardiology with organizing this Congress. Professor G. Nylin is the President of the Congress and Dr. Karl Erik Grewin the General Secretary.

The Congress will take place in Stockholm, from September 10th to 14th, 1956. The site of the scientific sessions and the exhibitions will be the Concert Hall.

The preliminary program for panel discussions and round-table conferences has been set up as follows:

Panel Discussion:

1. Etiology and Pathogenesis of Arteriosclerosis
2. Isolated Atrial and Ventricular Septal Defects
3. Pulmonary Hypertension
4. Cardiac Output and Its Regulation
5. Acquired Aortic Stenosis
6. Circulation in Hypothermia
7. Organic Peripheral Arterial Disease

Round-Table Conferences:

1. Treatment of Essential Hypertension
2. Treatment of Paroxysmal Arrhythmias and Other Ectopic Rhythms
3. Phonocardiography
4. Indications and Hazards of Heart Catheterization and Angiocardiography

An additional item to be discussed will be:

The Applicability of the Roentgenological Heart Volume Determination.

We have deliberately refrained from including the whole modern cardiology in this program, selecting instead a few items which we thought could be of interest. Other items will in all probability be discussed in submitted papers to be read at the Congress.

The Congress will be open in the first place to members of the National Heart Societies affiliated with the European Society of Cardiology. As far as space allows, it will also be open to other doctors interested in cardiology, both in Europe and else where.

Speakers at the panels and round-table conferences will be chosen by invitation.

Those who wish to submit papers to be read at the Congress should, according to the decision taken in Washington, September 1954, by the General Assembly of the European Society of Cardiology, send their papers to the National Society of the country concerned. Every National Society has to make a first selection and send them to the Secretary General with its recommendations or comments. From countries, where no national society of cardiology has been founded yet, the papers should be sent directly to the Secretary General, address: Södersjukhuset, Stockholm S., Sweden. The Program Committee of the Congress will then make the final selection.

The preliminary program and the application forms will be sent out towards the end of this year and give further information. The deadline for sending papers to the Secretary General will be *April 1, 1956.*

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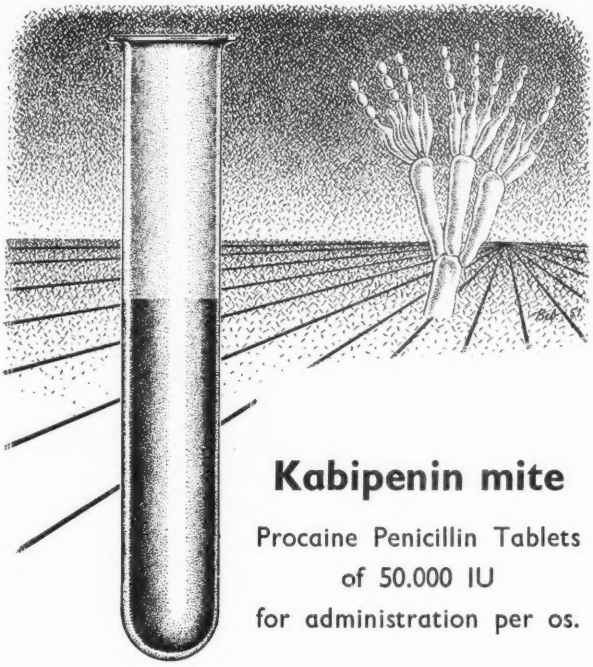

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Can Peroral Penicillin Treatment Substitute Parenteral Treatment in Acute Otitis? (Adolf Thulin – Sw. Med. Journal No. 23, 1951, p. 1440.)

On the Dosage of Procaine Penicillin Oral Tablets. (E. Nyman & A. Svanborg – Sw. Med. Journal No. 32, 1951, p. 1893.)

Scarlatina Treated at Home (Leena Leisti & J. Wickström – Nordisk Medicin No. 37, 1951, p. 1367.)

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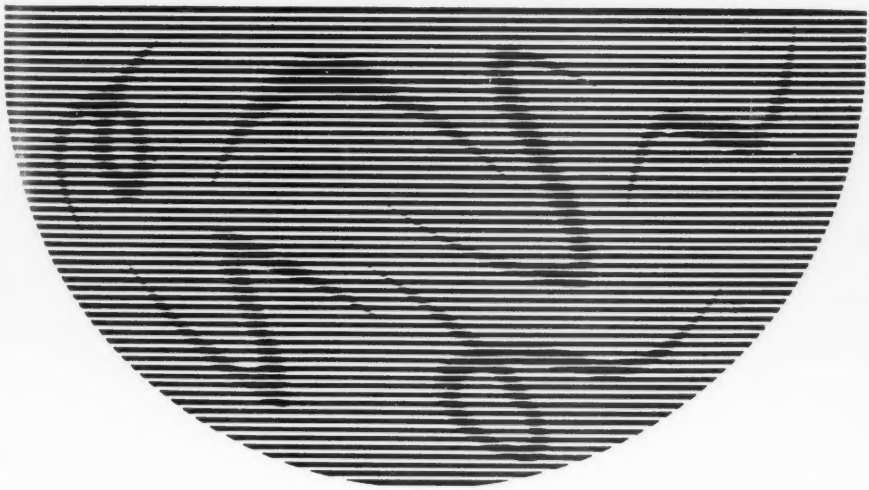

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